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# GIANT CELL PNEUMONIA OF INFANCY AS A MANIFESTATION OF VITAMIN A DEFICIENCY

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Giant cell pneumonia (*Riesenzellenpneumonie,* Hecht;[1] *bronchopneumonie à plasmodes,* Masson and Paré[2]) is a rare pathologic condition occurring in children, usually between the ages of 6 months and 2 years. It most commonly follows measles but may occur as a sequel to other infectious diseases or in association with tuberculosis. There does not appear to be anything to distinguish it clinically from other long-drawn-out, diffuse pneumonias. Histologically, one finds a greater or lesser number of giant cells in alveoli; often they are extremely numerous (fig. 1 *A*). Careful examination shows that there is a peculiar transformation of the alveolar lining membrane, with thickening, hyalinization and coalescence of the lining cells (fig. 1 *B* and *C*). The lesions have been described in detail by Hecht,[1] and their development has been studied by Masson and Paré.[2] Karsner and Meyers,[3] on reconstructing the giant cells, observed that

> what appeared to be a number of giant cells in a given slide ultimately were connected and formed part of a large syncytial mass extending through a large number of alveoli and infundibula. . . . *they were . . . a part of the alveolar epithelium* [italics mine], showing attachments to the alveolar wall in various places. When they lay free in the alveolar space there was no epithelium between them and the alveolar wall.

In short, the giant cells are metaplastic epithelial cells. Moore and Gross,[4] in Karsner's laboratory, questioned the existence of giant cell pneumonia as a pathologic entity. They thought that certain multinucleated protoplasmic masses which they believed were "formed by fusion of hyalinized exudate . . . and composed of degenerated red cells, leukocytes, lymphocytes, strands of fibrin and desquamated

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From the wards and St. Agnes Guild Laboratories of the Children's Hospital.

1. Hecht, V.: Beitr. z. path. Anat. u. z. allg. Path. **48**:262, 1910.
2. Masson, P., and Paré, L.: Ann. d'anat. path. **8**:13, 1931.
3. Karsner, H. T., and Meyers, A. E.: "Giant-Cell Pneumonia," Arch. Int. Med. **11**:534 (May) 1913.
4. Moore, R. A., and Gross, P.: Giant Cells in Inflammation of the Lung in Children, Am. J. Dis. Child. **40**:247 (Aug.) 1930.

epithelial cells" were similar to those observed by Karsner and Meyers. After careful examination of their photomicrographs I believe that they were mistaken in this opinion, that among their group of cases of pneumonia with giant cells they did not have a case of the Hecht-Masson type and that the lesion they described was entirely different from that here considered.

The etiology of the condition has remained hypothetic. It was early considered that aspiration of membrane from the upper respiratory tract might be the cause. Masson and Paré could only suggest a peculiarity in tissue response inherent in the condition of infancy. I wish to suggest in this paper that the fact that the alveolar lesion is a metaplasia of epithelium gives a lead to a possible explanation, namely, vitamin A deficiency. For cogent evidence that this is the true explanation one must turn to an examination of the respiratory tubes.

Hecht described a great increase in the number of layers of cells in the bronchioles and bronchi. In some cases there were giant cells on the surface and in 1 case in the epithelium. According to Masson and Paré, the bronchiolar epithelium is at first cuboidal or cylindric, with patches of desquamation. Subsequently, with continuing desquamation, several cylindric cells fuse, forming small triangular multinucleated cells embedded among their neighbors. The plasmodia, as Masson and Paré called these giant cells, grow outward along the surface, remaining flat, adhering to the basal layer and by degrees replacing the bronchial epithelium. Eventually the bronchioles are scarcely recognizable; there is no more cylindric epithelium, the wall consisting of discontinuous plasmodia. In the larger bronchioles and bronchi the epithelium is pleomorphic. In places it is ciliated, and elsewhere, of a stratified, pavement type or else covered with plasmodia. Masson and Paré built up this sequence from observations in various parts of the lung. Karsner and Meyers also noted giant cells in numerous places in the bronchiolar epithelium. In one they saw a mitotic figure.

I have no new observations to make on the lesions in the air sacs but would focus attention on those in the respiratory tubes. Through the cooperation of Drs. Robert F. Rorke, Pierre Masson, S. Burt Wolbach, Alwin M. Pappenheimer, Beryl Paige and Howard Karsner I have been able to study 5 cases of giant cell pneumonia. These cases are now presented in detail.

## REPORT OF CASES

CASE 1 (from the Children's Hospital of Winnipeg, unpublished).—Mary N., born at term and nursed to the age of 4½ months, was first admitted to the hospital at 4 months, with florid syphilis. She was treated with acetarsone and mercury.[5] Her evidence of syphilis disappeared slowly. At 5 months she had a

5. Davidson, A. M., and Birt, A. R.: Canad. M. A. J. **34**:33, 1936.

high fever for fifteen days and was critically ill. There were a few pus and blood cells in the urine. At 6½ months she was discharged; the Wassermann reaction of the blood was negative and the general condition improving. The patient was readmitted at 7 months with pyoderma, nasal discharge and conjunctivitis. The infection cleared up; she made good progress. She was discharged at 8½ months, the Wassermann reaction of the blood again negative. From this time on she made a steady gain in weight and vigor. Acetarsone and mercury were continued to the age of 15 months. At that time the child had a slight cold and low fever. At 16 months she was readmitted with spreading bronchopneumonia and high fever. The general nutritional state appeared good; the weight was 25¾ pounds (11,680 Gm.). The pneumonia continued to spread; the temperature remained high. There was nasal and aural discharge. The cough became extremely harsh. The patient died twenty-six days after admission, aged 17 months.

The diet had been as follows: from birth to 4½ months, breast milk; 4½ to 6½ months, half skimmed boiled milk, with ½ teaspoonful of cod liver oil except when there was a fever; 6½ to 7 months, pasteurized whole milk and water; 7 to 8½ months, boiled whole milk and 1 teaspoonful of cod liver oil a day; 8½ months to a year, 40 ounces (1,183 cc.) of whole pasteurized milk daily, with small additions of soups after a year. During her last illness she had 30 ounces (887 cc.) of boiled skimmed milk, sugar and water for ten days and, for the last twenty days, an addition of 1 ounce (3.7 cc.) of 20 per cent cream a day. The digestion appeared to be good.

*Postmortem Observations.*—Gross Examination: This was done three hours after death. While there was evidence of recent loss of weight, subcutaneous and perivisceral fat was still present in quantity. The fat was almost white. The following organs were grossly normal: the brain; the thyroid; the heart, 75 Gm.; the liver, 495 Gm.; the spleen, 45.8 Gm.; the pancreas; the adrenals, right 3.3 Gm. and left 3.6 Gm.; the kidneys, right 76.5 Gm. and left 69.5 Gm., and the uterus and ovaries. From the upper pole of the right lobe of the thymus (4.8 Gm.) a cord of tissue the size of a match stick passed up behind the thyroid. The intermediate cleft of the pituitary was distended with colloid. The left lung (211.2 Gm.) was firm and adherent everywhere except for the lappet of the upper lobe. Externally the lung was mottled, dull gray and red. On section it was drier than is usual with bronchopneumonia. The cut surface was made up of confluent gray patches outlined and interspersed with red. The right lung (197.7 Gm.) was markedly emphysematous anteriorly. The posteroinferior part of the upper lobe was firmly consolidated, and the posterior part of the lower lobe was shotty with gray nodules of consolidation. A paratracheal lymph node to the right of the midtrachea was a soft reddish spheroid 22 mm. in diameter.

Microscopic Examination: There were no spirochetes in any tissue. The tissues of the esophagus, pancreas, parathyroids, adrenals, heart, uterus and vagina were histologically normal. The pituitary contained a large mass of colloid in the intermediate cleft. The cells of the anterior lobe did not appear smaller than usual. The thyroid was made up of small irregular vesicles, with a high pale cuboidal epithelium and practically no colloid, in an abundant vascular stroma. The thymus consisted of connective tissue with small collections of loosely arranged lymphocytes and very few extremely small corpuscles. An unusual number of primordial follicles in the ovary contained more than one ovum each. In the liver hemosiderin was present, and there was foamy degeneration with shrinking of the cells about the central veins. The spleen contained an abundance of hemosiderin. In the kidney an occasional glomerulus was fibrosed, a rare tubule

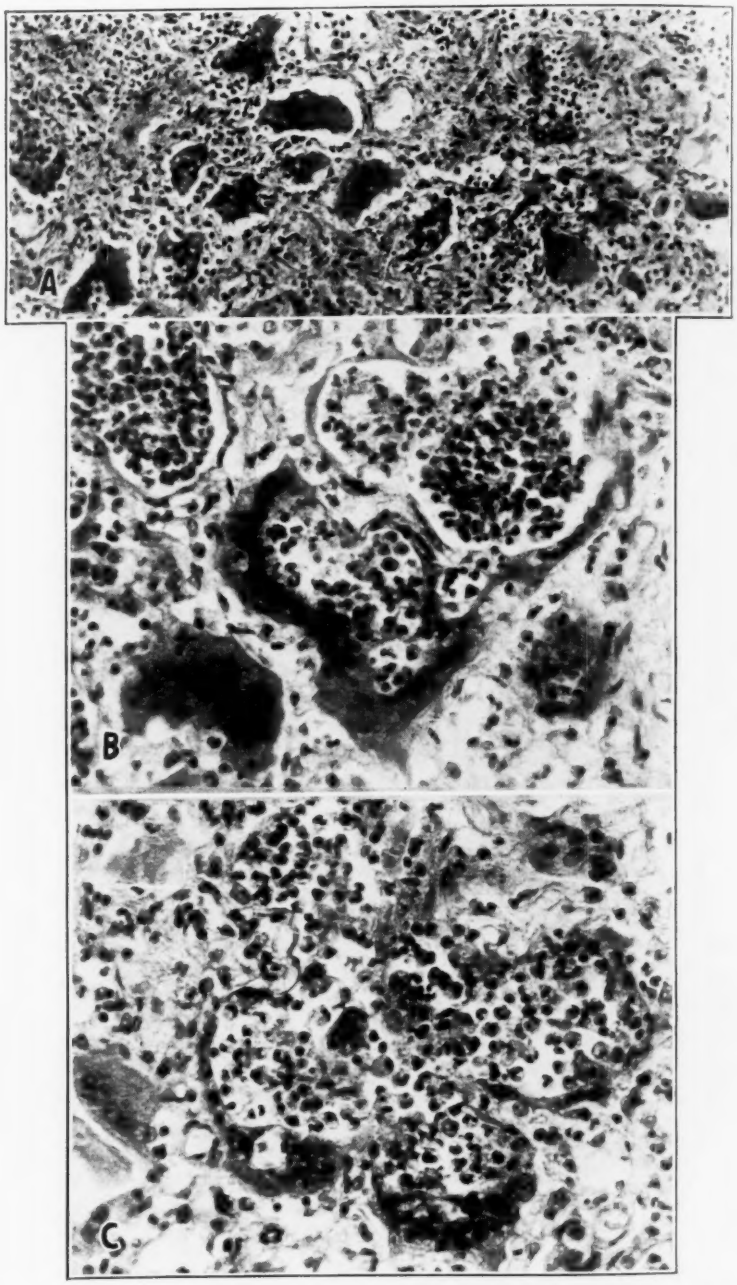


Fig. 1 (case 1).—*A*, many giant cells are seen in the lung. Magnification, × 100. *B* and *C*, lung tissue showing the transition of alveolar membrane from a dense fine line through coalescent low epithelium to a multinucleated syncytial mass. Magnification, × 275.

contained albumin and one minute superficial wedge of interstitial fibrosis was seen. The epithelium of the pelvis had largely been shed. What remained was not hyperplastic or metaplastic. The lungs, from which Staphylococcus pyogenes aureus was grown, were the seat of marked giant cell pneumonia (fig. 1). The large paratracheal lymph node contained a few giant cells.

The histologic picture of the upper respiratory tract strongly suggested vitamin A deficiency. The vocal cord, normally at this age a thin stratified epithelium of peculiarly translucent appearance, was keratinized; there were papillary downgrowths of the deep surface and numerous mitotic figures (fig. 2*A*). The mucous membrane of the false vocal cord, which normally, according to my observations, is either a thin stratified or a respiratory type of epithelium at this age, was likewise thickened and keratinized, as were ducts of mucous glands. The posterior surface of the epiglottis showed a similar change. In places mitotic figures were present in large numbers (fig. 2*B*). The trachea, at all levels examined, had entirely lost its columnar, ciliated and goblet cell border. In place of this the superficial cells were flattened, with spaces between them, and the whole membrane was thinned. The vocal ventricle, always normally lined with respiratory epithelium, had undergone a change similar to that of the trachea (fig. 2*C*). Here the superficial epithelium was seen being cast off in the form of syncytial masses. The metaplastic squamous epithelium appeared to be advancing on the normal epithelium. The cells of the mucous glands of the trachea and larynx were flattened out along the periphery and contained little cytoplasm. Their nuclei were small and deeply staining and showed a tendency to clump together in giant cell formation. Wilson and Dubois's [6] description of the tracheal glands in their case of vitamin A deficiency appears to be identical with this.

The bronchioles showed the changes described by Masson and Paré: condensation of the cuticular border, coalescence of groups of superficial cells and areas of stratification.

At the junction of bone and cartilage there were lesions which I am unable to interpret. In the ribs there was tremendous increase in depth of the zone of hypertrophic cartilage but no osteoid, while at the lower end of the tibia the zone was narrow, and on it was laid a more or less continuous layer of bone. These changes suggest a general metabolic upset of undetermined nature.

In summary, in an infant of 17 months with giant cell pneumonia, the epithelium of the larynx, trachea, bronchi and bronchioles had undergone metaplasia similar to that associated with vitamin A deficiency. Hemosiderin was present in the liver and the spleen. The bones were the seat of a type of lesion suggesting a general metabolic disease.

Case 2 (from the pathologic department, University of Montreal).—This formed the basis for the report by Masson and Paré to which reference has already been made. Gisele C., aged 9 months, was admitted to Sainte-Justine Hospital on Jan. 21, 1930, on account of a cough of one month's duration and dyspnea. There had been an unidentified rash at the beginning of illness. On the child's admission she had bilateral cervical adenitis, pulmonary signs suggesting tuberculosis with superadded pneumonia and beading of the ribs. Signs of tuberculous meningitis developed a few days later. The patient died on February 16. At autopsy were observed miliary tuberculosis, rickets, caseous tuberculosis of the cervical, tracheobronchial and mesenteric lymph nodes, bilateral otitis media and bronchopneumonia with bronchiectasis.

6. Wilson, J. R., and Dubois, R. O.: Keratomalacia in an Infant, with Postmortem Examination, Am. J. Dis. Child. **26**:431 (Nov.) 1923.

Sections of the lungs only were available for study. These were the seat of tuberculosis and extensive giant cell pneumonia. The alveolar lesions are excellently illustrated in Masson and Paré's paper. The bronchioles were the seat of extensive

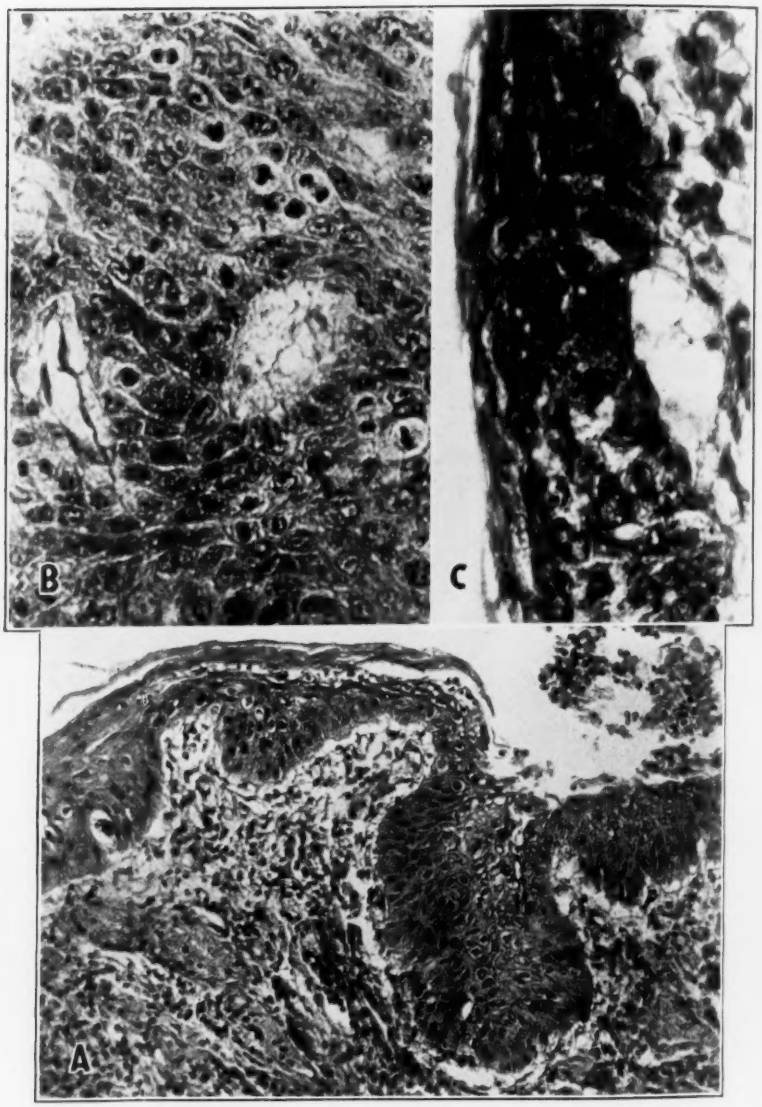


Fig. 2 (case 1).—*A*, keratinization and downgrowth of the vocal cord. Magnification, × 140. *B*, many cells in mitosis are seen in the epiglottis. Magnification, × 400. *C*, keratinizing squamous metaplasia of the vocal ventricle. Magnification, × 600.

desquamation, giant cell formation and metaplasia to a transitional but not squamous type of epithelium (fig. 3 *A* and *B*). The bronchiolar lesion suggested in part incomplete repair of vitamin A deficiency and in part production of this deficiency.

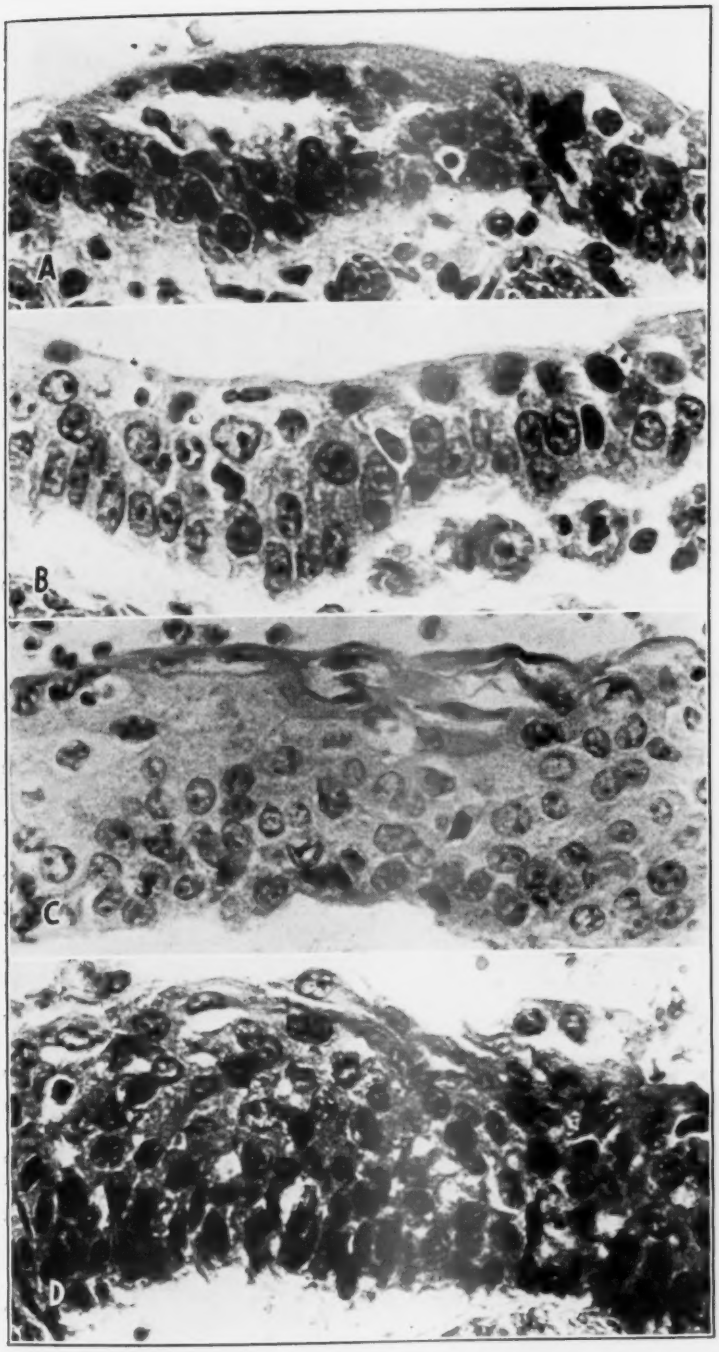


Fig. 3.—In *A* (case 2) the columnar or cuboidal single-layered epithelium of a small bronchiole is replaced by low stratified epithelium. There is coalescence of some of the surface cells, with the production of a plasmodium or giant cell. Magnification, × 600. *B* (case 2) shows stratification of epithelium in another bronchiole. The appearance suggests incomplete deficiency of vitamin A. Magnification, × 600. *C* (case 3) reveals stratification and partial squamous transformation in a small bronchiole which normally is lined by a single layer of columnar or cuboidal cells. Magnification, × 600. In *D* (case 4) still greater squamous metaplasia is seen in a bronchiole of about the same diameter as those in *A*, *B* and *C*. Magnification, × 600.

Case 3 (from the pathologic department, Harvard Medical School).—This case formed the basis for Karsner and Meyers' study,[3] published in 1913. The following summary is extracted from their report. Victoria A., an Italian girl of 18 months, was admitted to the Children's Hospital, Boston, on Sept. 18, 1911, and died there on October 2. As an infant she had been fed equal parts of milk and water. In August 1911 she had had what was probably pneumonia, from which she recovered. On September 13 she became acutely ill with vomiting, cough, fever and moderate diarrhea. On admission she was suffering from extreme rickets and diffuse bronchopneumonia. The condition progressed steadily downward to death. Postmortem observations, apart from those of the lungs, showed that the heart, pancreas, stomach, intestines and adrenals were normal; that the liver had cloudy swelling and fatty metamorphosis; the spleen, acute enlargement; the kidneys, cloudy swelling, and the thymus, fibrosis. Staph. pyogenes aureus was grown in cultures of material from the lungs, which were the seat of patchy bronchopneumonia of giant cell type.

At Dr. Wolbach's laboratory I examined sections of the organs just mentioned. The pancreas and what little there was of pelvic mucosa attached to the kidney showed no metaplasia. Sections of spleen and liver stained for iron were not available. Karsner and Meyers have illustrated the giant cell lesion of the air spaces, and I have quoted their description of their reconstruction of these cells. Figure 3*C* illustrates the bronchiolar lesion. The process of transformation into squamous epithelium is farther advanced than in case 2.

Case 4 (from the pathologic department, Presbyterian Hospital, and the College of Physicians and Surgeons of New York; unpublished).—Irwin H., a Negro boy of 9 months, was admitted to Presbyterian Hospital on March 11, 1914, and died on March 15. No early history is available. The baby had had pneumonia a month and diphtheria a week before admission. For four days he had been feverish and had vomited. On his admission there were signs of bronchopneumonia; he had a furuncle on the scalp and marked evidence of active rickets. The urine contained occasional hyaline casts, epithelial cells and leukocytes. The child died four days after admission.

*Postmortem Observations.*—Gross Examination: Bronchopneumonia involved the lower lobe of the left lung and the upper and lower lobes of the right. The thymus was small. The other viscera showed no grossly pathologic change.

Microscopic Examination: I examined the pancreas, liver, kidney, spleen and lung. In the first three there was no evidence of vitamin A deficiency. The splenic sections were not stained for iron. In the lung the giant cell formation was marked, corresponding in type to that already illustrated. The bronchioles were the seat of squamous epithelial metaplasia (fig. 3*D*). The ducts of the bronchial glands showed a similar type of lesion, with marked hyperplasia (fig. 4*A*).

Case 5 (from the pathologic department, Babies Hospital, and the College of Physicians and Surgeons of New York; unpublished).—Felder R., a Negro boy of 22 months, was admitted to the Babies Hospital on May 31, 1931 and died on June 10. He was born at term; the weight at birth was 6 pounds and 4 ounces (2,835 Gm.). The infant was never breast fed but was given a formula of whole milk and dextrimaltose. Cereal was added at the age of 5 months and vegetables at 6 months, and at 1 year the child was given a general diet. Cod liver oil had been started at about 1 month, and a teaspoonful was given daily from 2 months. Orange juice had been given from 6 weeks. The infant had

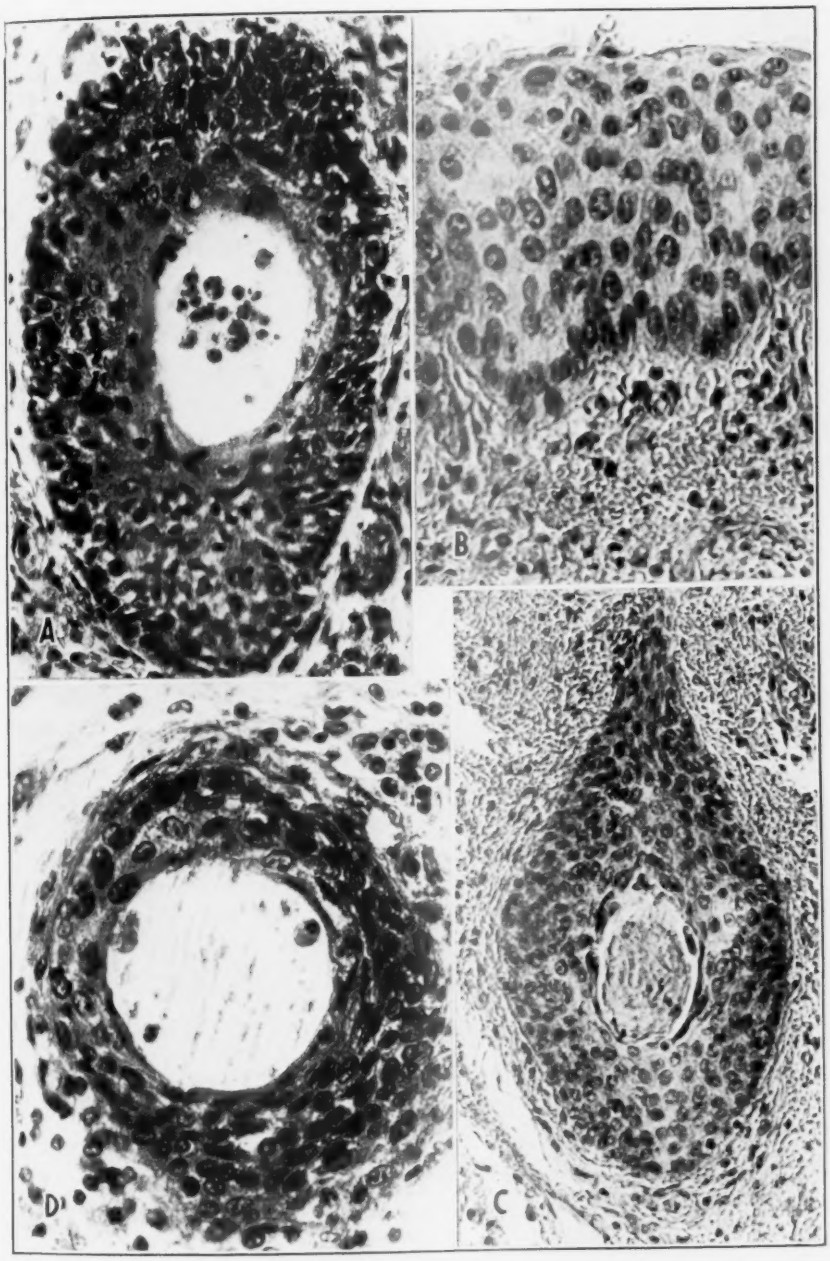


Fig. 4.—*A* (case 4) shows a metaplastic duct of a seromucous gland. Normally the lining is a single layer of cuboidal cells. Magnification, × 300. *B* (case 5), squamous metaplasia and hyperplasia of tracheal mucosa. Magnification, × 400. *C* (case 5), keratinizing squamous metaplasia of the duct of a tracheal seromucous gland. Magnification, × 250. *D* (case 5), metaplasia of the duct of a seromucous gland of a small bronchial tube. Magnification, × 400.

had frequent colds and continuous rhinorrhea. His appetite had always been poor. Two other children in the family had died of bronchopneumonia.

On May 16 measles developed. The patient was then admitted to the Babies Hospital suffering from otitis media, cervical adenitis and bronchopneumonia. The Wassermann reaction of the blood was positive, and a roentgenogram of the long bones showed evidence of syphilis. There was no clinical or roentgen evidence of rickets. The child's condition became progressively worse. Spreading streptococcic cellulitis developed from the area of the adenitis. The otitis and pneumonia persisted. The boy died on June 10, twenty-six days after the onset of measles.

*Postmortem Observations.*—Gross Examination: There was no evidence of rickets. The lungs were the seat of diffuse patchy bronchopneumonia, but much normal-appearing lung tissue was present. The remaining viscera were not remarkable; the heart weighed 58 Gm., the thymus 16 Gm., the spleen 44 Gm., the liver 375 Gm., the adrenals 5 Gm. and the kidneys 112 Gm.

Microscopic Examination: I examined tissues of the pituitary, thyroid, thymus, adrenals, pancreas, heart, submaxillary salivary gland, liver, kidney without any of the pelvis, spleen and prostate and did not find evidence of vitamin A deficiency in them. The thymus consisted essentially of connective tissue with minute islands of thymus cells and practically no Hassall corpuscles. There was hemosiderosis of the spleen. The lungs were the seat of patchy desquamative bronchopneumonia, with small islands of typical giant cells. The trachea showed marked squamous cell metaplasia (fig. 4*B*), as did the ducts of its glands (fig. 4*C*). The bronchiolar epithelium was not metaplastic, but the ducts of some of the bronchiolar mucous glands were the seat of well advanced metaplasia (fig. 4*D*).

I think this an important case. Dr. Paige [7] in her original examination classified the pulmonary lesion as bronchopneumonia with giant cells rather than as giant cell pneumonia and did not feel that the case could be placed under the latter heading. She supplied it to me as the nearest approach to a case of Hecht's giant cell pneumonia she had seen at the Babies Hospital. As she pointed out, even the sections showing the greatest number of giant cells contained few as compared with those shown in Hecht's paper. There were only occasional groups of them, infinitely fewer than in cases 1, 2, 3 or 4. On the other hand, they were of the same type as in these cases. The trachea, tracheal glands and bronchial glands showed what are considered classic signs of vitamin A deficiency. This case then serves to prove that, even when the Hecht-Masson type of giant cell formation is extremely limited, metaplasia of the respiratory tubular epithelium is present.

## COMMENT

Such are the facts as they have been observed. The epithelium of the air tubes in every case of giant cell pneumonia is hyperplastic and metaplastic to a greater or lesser degree. Is this due to vitamin A deficiency? On what histologic evidence can one make an assured diagnosis of this deficiency? The observation of keratinizing squamous epithelium undermining nonsquamous epithelium, as described by

7. Paige, B.: Personal communication to the author.

Wolbach and Howe,[8] would be such evidence. So too would be keratinizing squamous metaplasia of more than one system. But when does metaplasia of part of a single system become such evidence?

Wolbach and Howe [9] and Blackfan and Wolbach [10] have emphasized the keratinizing nature of vitamin A metaplasia. In the experimental animal completely deprived of vitamin A, the metaplasia begins as small syncytial foci which, transforming into squamous keratinizing epithelium, spread out under the somewhat atrophic neighboring epithelium. From the outset the metaplastic epithelium is keratinized. Whether this is true in man is open to question. In all of Blackfan and Wolbach's cases in which the diagnosis was vitamin A deficiency in infants, the metaplasia was described as keratinizing. Altschule,[11] examining the bodies of infants who had suffered from congenital obstruction of the biliary passages, included as evidence of vitamin A deficiency examples of epithelium which had undergone stratified squamous metaplasia with slight or no keratinization. I judge from his descriptions that he believed metaplasia may precede keratinization. Sweet and K'ang's [12] observations on children and adults with keratomalacia strengthen this view. They noted keratinizing metaplasia in some organs, either squamous or partly squamous metaplasia in others and, in addition, combinations of these changes in the same organ. Thatcher and Sure [13] in the report of a case also recorded mild hyperplasia of the renal pelvis with metaplasia elsewhere. These observations make less exact the definition of the lesions that have been accepted as due to vitamin A deficiency, but they do not answer the original question, "When does metaplasia of a single system become sufficient evidence on which to base an assured diagnosis of vitamin A deficiency?"

It has long been held that chronic mechanical or physical irritation, chronic infections and even influenzal infection of fairly short duration may produce metaplasia. If none of these factors is present and squamous stratified metaplasia appears in an epithelial surface, the metaplasia may with reasonable assurance be ascribed to vitamin A deficiency. If infection is present one cannot with certainty say more

8. Wolbach, S. B., and Howe, P. R.: J. Exper. Med. **42**:752, 1925.

9. Wolbach, S. B., and Howe, P. R.: Vitamin A Deficiency in the Guinea-Pig, Arch. Path. **5**:239 (Feb.) 1928; J. Exper. Med. **57**:511, 1933; footnote 8.

10. Blackfan, K. D., and Wolbach, S. B.: J. Pediat. **3**:679, 1933.

11. Altschule, M. D.: Vitamin A Deficiency in Spite of Adequate Diet in Congenital Atresia of the Bile Ducts and Jaundice, Arch. Path. **20**:845 (Dec.) 1935.

12. Sweet, L. K., and K'ang, H. J.: Clinical and Anatomical Study of Avitaminosis A Among the Chinese, Am. J. Dis. Child. **50**:699 (Sept.) 1935.

13. Thatcher, H. S., and Sure, B.: Avitaminosis: Pathologic Changes in the Tissues of the Albino Rat During the Early Stages of Vitamin A Deficiency, Arch. Path. **13**:756 (May) 1932.

than that the metaplasia may be due to vitamin A deficiency or to the infection. Possibly the process is the same in both cases, an infectious agent producing a local deficit in the vitamin. This possibility requires further consideration.

Passey, Leese and Knox,[14] noting the frequent occurrence of bronchiectasis with metaplasia in rats, attempted to discover if the metaplasia was due to vitamin A deficiency. In their experimental animals metaplasia of the respiratory tract was common. It proceeded farther in vitamin A–deficient animals, and keratinization was almost, but not entirely, confined to them. The metaplasia of vitamin A deficiency and that of infection were otherwise indistinguishable, which suggests that they may be the same, infection producing a local or general depletion. The authors did not report on epithelial surfaces outside the respiratory tract.

Goldblatt and Benischek,[15] studying vitamin A deficiency in rats, thought that when inflammation was present the epithelial metaplasia was usually more severe.

When Blackfan and Wolbach[10] reported 13 cases of vitamin A deficiency in infants, they were faced with offering some explanation for the occurrence of the disease in infants who had had "an amount of A usually regarded as being protective for young infants." There were 7 such cases among 11 in which autopsies were performed. In 2 the condition could be explained as due to faulty absorption, 1 patient having congenital atresia of the bile ducts and the other chronic diarrhea. To account for the involvement in the other 5 cases, Blackfan and Wolbach offered the working hypothesis that "a chronic generalized infection" produced a "grave metabolic disturbance interfering with proper absorption, storage and utilization of vitamin A or its precursor, carotene." I am not certain how Blackfan and Wolbach would define either "chronic" or "generalized" in this connection. The symptoms in the 5 cases lasted thirteen days, three and one half months, six weeks, five weeks and somewhat over four weeks, respectively. The infections recorded were extensive bronchopneumonia with bronchiectatic cavities in every case, in 1 instance complicated by empyema and in 1 by empyema, otitis media and terminal ulcerative colitis and in 1 associated with profuse nasal discharge. In any event, it is evident that the authors conceived of these infections as having a general effect on the whole organism, with consequent deficiency of the whole organism. After careful study of their material and of the data available they felt that they could not say whether the alterations in the epithelial cells of the respiratory tract preceded the infection or followed it. Their

14. Passey, R. D.; Leese, A., and Knox, J. C.: J. Path. & Bact. **42**:425, 1936.

15. Goldblatt, H., and Benischek, M.: J. Exper. Med. **46**:699, 1927.

*Distribution of Epithelial Lesions in Reported Cases of Vitamin A Deficiency**

| Case No. | Infection | Eyes | Respiratory Tubes | Pharynx | Esophagus | Salivary Glands | Kidney Pelvis | Uterus | Pancreas | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Cases in Which Diet Was Deficient** | | | | | | | | | |
| 1. | Cases of Blackfan and Wolbach [10] | | | | | | | | | |
| 1 | Pneumonia | ++++ | ++++ | ..... | ..... | ++++ | ++++ | ++++ | ++++ | |
| 4 | Pneumonia | ++ | +++ | ..... | ..... | ..... | ++ | ..... | ..... | Treated 5 weeks |
| 10 | Pneumonia | ++++ | ++++ | ..... | ..... | ++++ | ++++ | ++++ | ++++ | |
| 13 | Pneumonia | ++++ | ++ | No section | No section | No section | No section | + | ..... | Autopsy in another hospital; atrophy of pancreas |
| | **Cases in Which Absorption Was Presumably Deficient** | | | | | | | | | |
| 9 | Slight bronchitis | ..... | + | ..... | ..... | ..... | + | ..... | ..... | Diarrhea |
| 11 | None | ..... | +++ | ..... | +++ | ..... | +++ | ..... | ..... | Atresia of bile ducts |
| | **Cases in Which Diet Was Good** | | | | | | | | | |
| 2 | Pneumonia | ..... | +++ | ..... | ..... | ..... | ..... | ..... | + | Atrophy of pancreas |
| 3 | Pneumonia | ..... | + | ..... | ..... | ..... | ..... | ..... | ..... | Atrophy of pancreas |
| 6 | Pneumonia | ..... | ++ | ..... | ++ | ..... | ..... | ..... | ..... | |
| 7 | Pneumonia | ..... | +++ | ++ | ..... | ..... | + | ..... | + | |
| 8 | Pneumonia | ..... | +++ | +++ | ..... | ..... | ..... | ..... | ..... | |
| | **Cases in Which There Were Atresia of Bile Ducts and Jaundice** | | | | | | | | | |
| 2. | Cases of Altschule [11] | | | | | | | | | |
| 2 | None | ..... | ++++ | ..... | +++ | ..... | ++++ | ..... | ..... | Same as in Blackfan and Wolbach's case 11 |
| 1 | None | ..... | ++ | ..... | ..... | ..... | ++ | ..... | + | |
| 5 | None | ..... | ..... | ..... | ..... | ..... | +++ | ..... | ..... | |
| 6 | None | ..... | ..... | ..... | ..... | ..... | +++ | ..... | ..... | |
| 4 | None | ..... | ..... | ..... | ..... | ..... | + | ..... | + | |
| 3 | None | ..... | ..... | ..... | ..... | ..... | + | ..... | ..... | |
| 3. | Cases of Sweet and K'ang [12] | | | | | | | | | |
| 14 | Postmeasles pneumonia | ++++ | +++ | ..... | +++ | ..... | ++ | ..... | ..... | |
| 4 | Postmeasles pneumonia | ++++ | +++ | ++++ | ..... | ..... | ..... | ..... | + | |
| 16 | Dysentery, tuberculosis | ++++ | +++ | ..... | ..... | ..... | ..... | ..... | ..... | |
| 1 | Pneumonia | ++++ | ++ | ..... | ..... | ..... | ..... | ..... | ..... | |
| 8 | Dysentery, terminal pneumonia | ++++ | ..... | ..... | ++ | ..... | ..... | ..... | ..... | |
| 10 | None | +++ | ++ | ..... | ..... | ..... | + | ..... | ..... | |
| 3 | Pneumonia | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | Keratomalacia earlier |
| 9 | None | ++++ | ..... | ..... | + | ..... | ..... | ++ | ..... | |
| 12 | Syphilis | ++++ | ..... | ..... | ..... | ..... | ..... | ..... | ..... | Pyuria |
| 13 | Pneumonia | ++++ | ..... | ..... | ..... | ..... | ++ | ..... | ..... | |
| 17 | None | ++++ | + | ..... | ..... | ..... | ..... | ..... | ..... | |
| 6 | Pulmonary tuberculosis | ++++ | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 3 weeks' treatment |
| 2 | Pulmonary tuberculosis | ++++ | ..... | ..... | ..... | ..... | ..... | ..... | ..... | |
| 5 | Pneumonia | +++ | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 3½ weeks' treatment |

* Although these data show the apparent frequency distribution of epithelial lesions, they cannot be considered complete since usually at autopsy only routine tissues were taken for examination. Sections 2 and 3 are arranged in the order of extent of the lesion. Sections 1 and 2 suggest a relationship between infection and degree of local lesion. Section 3 does not bear this out. Note the severity of the lesion associated with measles.

data do show that metaplasia was farthest advanced in the system that was the seat of infection (table, section 1). In contrast are the data set out in section 2 of the table, compiled from Altschule's report of vitamin A deficiency associated with congenital atresia of the bile ducts. Here there was no suspicion that chronic infection caused either local or general depletion. The assumption was that as a result of the absence of bile or some of its constituents from the intestinal tract there was faulty absorption of vitamin A. The deficiency would be a general one. In the absence of pneumonia the respiratory tract is not the seat of more advanced metaplasia than are the other tracts.

This concept of an infection causing a local depletion gains no support from Sweet and K'ang's study. In patients with keratomalacia and chronic or acute pulmonary disease they repeatedly failed to find metaplasia of the respiratory tract, e. g., in cases 2, 3, 4, 6 and 13. Their data are set out in section 3 of the table. There is a striking contrast between the observations of Blackfan and Wolbach and those of Sweet and K'ang. In the cases studied by the former authors, when the eyes were involved, metaplasia in other viscera paralleled that in the eyes; in 3 cases of the latter authors, keratomalacia was the only sign of vitamin A deficiency and in 6 cases the lesions elsewhere were extremely slight. It is open to question whether this difference in experience only reflects the variation in random sampling or whether in Sweet and K'ang's cases there was a second factor that speeded up the pathologic changes in the eyes.

The concept of local depletion of the vitamin by infection obviously does not exclude the production of general depletion by the same means. It is conceivable that all available supplies, if they are low, may be used up in trying to repair the damage at one point. So may one explain the early lesions outside the respiratory tract in Blackfan and Wolbach's cases 2 and 7. It appears that it is not at the point of most violent inflammation that the greatest evidences of depletion are observed but rather in those surfaces over which the products of inflammation flow.[16]

So much for local depletion. Its cause is an open question. The matter of general depletion by disease must also be considered. It has long been held by those with an extensive acquaintance with keratomalacia, particularly in the Orient, that an acute infection other than that of the eyes may kindle the disease. The common precipitating condition, however, has been diarrhea. This presumably may interfere with absorption as well as cause depletion as an infection. At times, as

16. If the current concept of night blindness as commonly due to vitamin A deficiency is valid, it is strong support for the idea that local deficiency of the vitamin can occur in the presence of considerable stores in the liver. The term "local deficiency" is used to mean, broadly, "insufficient for the requirements of a particular tissue in a particular state of activity."

Pillat [17] pointed out, diarrhea is symptomatic of vitamin A deficiency rather than a cause of it. The occurrence of keratomalacia following the onset of diarrhea cannot be considered as proof that an infection has caused depletion of the vitamin or that infections in general will do so. Blackfan and Wolbach pointed out that keratomalacia preceded the onset of infection in some of their cases. Although Sweet and K'ang expressed the opinion that such diseases as tuberculosis, syphilis, kala-azar and pneumonia might reduce the stores of vitamin, they did not offer concrete evidence of depletion by infection. In the cases reported in detail keratomalacia frequently preceded infection.

A different approach to the relation between infection and vitamin A depletion has been made by assaying the liver for its content of the vitamin after death. So far the results of these extensive investigations have brought out only two facts: that if the method of assay gives an accurate measure of the reserves of the vitamin at the moment of death, then those reserves vary over a wide range during health and during all sorts of diseases and that the reserves are low per gram of liver at birth and in the first few months of infancy. It certainly is not yet clear that infection per se or specific infections regularly lower the hepatic reserve. Just as there is no convincing proof that large doses of vitamin A will prevent infections, so there is no proof that infections will deplete the body of the vitamin.

One cannot then give a categorical answer to the question: "In the presence of infection when does metaplasia of a single system become sufficient evidence on which to base an assured diagnosis of vitamin A deficiency?" For we do not know whether infection produces metaplasia by causing local or general depletion of the vitamin or by some entirely unrelated process. Until this point is cleared up, the diagnosis of vitamin A deficiency in such cases as Blackfan and Wolbach's cases 2, 3, 6, 7 and 8 and the cases here reported must be considered as not proved. In the present cases the basis on which a diagnosis of vitamin A deficiency might be made is, I hope, evident from the illustrations. The bases are firmest in cases 1, 4 and 5. Few sections were available in cases 2, 3 and 4, and many tissues were missing.

The similar age incidences of vitamin A deficiency and giant cell pneumonia lend color to the assumption that the diseases are the same. Dr. Wolbach has offered a strong argument against this assumption. He told me that in all his experience (and it is a good deal wider than his reported cases indicate) he has never seen giant cell pneumonia in infants dying with vitamin A deficiency, even though pneumonia is the commonest cause of death. There are two points against accepting this as final proof that the two diseases are not related. First, giant cell

17. Pillat, A.: Does Keratomalacia Exist in Adults? Arch. Ophth. **2**:256 (Sept.); 399 (Oct.) 1929.

pneumonia usually follows measles and less frequently comes after one of the other contagious diseases or accompanies tuberculosis. In none of Wolbach's reported cases had the patient suffered from any of these diseases. It is probable that if infection is a factor in vitamin A deficiency the response will vary with the infecting agent. On the other hand, in Sweet and K'ang's cases 4 and 14 the deficiency followed measles, and in neither one was giant cell pneumonia reported, although, interestingly enough, the lesions of vitamin A deficiency were the most extensive in the series of these authors. The second point is that Wolbach has never reported alveolar metaplasia either in subjects with experimental vitamin A deficiency or in infants with this deficiency. Yet such keratinizing metaplasia does occur. Passey, Leese and Knox recorded it in 1 rat given a full diet but with infection and in 2 mice given a vitamin A–deficient diet. If keratinizing metaplasia occurs, then why not the nonkeratinizing type? And if nonkeratinizing metaplasia and hyperplasia of other epithelial surfaces are accepted as evidence of vitamin A deficiency,[18] then why should not such metaplasia of the alveoli be so accepted?

The dietary histories in cases 1 and 5 appear to be against the diagnosis of vitamin A deficiency. In case 1 the intake of the vitamin was perhaps not optimal but was as much as many an infant receives. In case 5 the child had received cod liver oil from about the age of 1 month. In case 1 the patient had had syphilis, boils, fever of undetermined nature and finally pneumonia lasting a month. In case 5 the infant had active syphilis, a history of frequent colds and a terminal illness lasting nearly a month. Did this combination of infections produce, as Blackfan and Wolbach phrased it, "a grave metabolic disturbance interfering with proper absorption, storage and utilization of vitamin A, or its precursor, carotene?" I do not know.

There is one last point of possible practical interest. Speaking of the relation between vitamin A and infection, Harris[19] said there is little to suggest that any benefit is likely to accrue from treatment of acute infections by vitamin A. He based this deduction on what appears to be a true concept of the course of infection in cases of primary vitamin A deficiency, namely, loss of local physical and chemical mechanisms of protection, invasion of nonresisting membranes by organisms and generalization of the infection. Once invading organisms have passed the frontier, closing it with vitamin A will not stop the ravaging organisms from destroying the patient. In this sense Harris' statement seems probably true. If, however, infection can cause local depletion, with the train of events that he described then following,

18. Altschule.[11] Sweet and K'ang.[12] Thatcher and Sure.[13]

19. Harris, L. J.; Innes, J. R. M., and Griffith, A. S.: Lancet **2**:614, 1932.

the administration of vitamin A in liberal amounts may well prove of value in treatment by allowing the epithelium to retain or to rebulid its local mechanisms of defense. This might explain the striking reduction in mortality from measles which Ellison [20] obtained when he treated patients with vitamins A and D. But Ellison's results have not been confirmed, while Degen,[21] recently reporting the pathologic visceral changes in 100 patients who died of measles, 85 under the age of 5 years, did not record any instances of giant cell pneumonia or hyperplasia or metaplasia of the respiratory tract, although 93 per cent of the patients had gross pneumonia. This is in contrast to Hecht's study of twenty-eight years ago, when among 162 cases of pneumonia in children he observed 27 instances of the giant cell type, in 19 of which the condition followed measles. Can the dietary changes of the last quarter of a century account for this difference, or is some other factor responsible?

## CONCLUSION

There is no conclusion. The hypothesis that the giant cells of giant cell pneumonia represent metaplasia of alveolar epithelium due to vitamin A deficiency cannot be proved by argument. Proof or disproof must await experiment. So, too, only experiment can answer the questions of whether infection can cause either local or general depletion of vitamin A and whether such depletion can be prevented by giving the vitamin during the course of infection. It is an interesting problem.

## SUMMARY

Five cases of giant cell pneumonia are reported, and the possibility that the giant cell formation is the result of vitamin A deficiency is discussed, though no conclusion is reached. The effect of infection on vitamin A depletion is also considered.

The photomicrographs in this article were taken by Miss Lizetta Nason, of the University of Manitoba Department of Pathology, by permission of Prof. William Boyd.

20. Ellison, J. B.: Brit. M. J. **2**:708, 1932.
21. Degen, J. A., Jr.: Am. J. M. Sc. **194**:104, 1937.

# EFFECTS OF WHOOPING COUGH ON TUBERCULOSIS

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Considerable data published in the past two decades relative to the effects of whooping cough on tuberculosis indicate that whooping cough is not as harmful in tuberculous children as commonly believed.

Pospischill,[1] in 1921, reported the results of clinical and postmortem studies of thousands of cases of whooping cough in Vienna. He noted that there were few patients with active tuberculosis among those who died, and rarely was tuberculosis the cause of death, even though it was common in Vienna. On the other hand, there were numerous nontuberculous pulmonary changes which might be mistaken clinically for tuberculosis. Some of these pathologic changes were bronchitis, peribronchitis, bronchiectasis, interstitial induration, bronchopneumonia and pleuritis. Similar pulmonary changes were described in detail by Feyrter.[2] Popischill concluded that he had never found a case in which the influence of whooping cough on tuberculosis could be proved. This conclusion was confirmed by other investigators[3] who had made clinical studies of large groups of cases of whooping cough.

The belief that whooping cough predisposes to miliary tuberculosis and tuberculous meningitis has been questioned by various investigators.[4] In an occasional case miliary tuberculosis or tuberculous meningitis may

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1. Pospischill, D.: Ueber Klinik und Epidemiologie der Pertussis, Berlin, S. Karger, 1921.

2. Feyrter, F.: Ueber die pathologische Anatomie der Lungenveränderungen beim Keuchhusten, Frankfurt. Ztschr. f. Path. **35**:213, 1927.

3. (*a*) Gabriel, E.: Pertussis und Tuberkulose, Jahrb. f. Kinderh. **142**:281, 1934. (*b*) Meyer, S., and Burghard, E.: Beitrag zur Klinik des Keuchhustens, Ztschr. f. Kinderh. **40**:103, 1925.

4. (*a*) Debré, R., and Cremieu-Alcan: Etude sur l'étiologie de la meningite tuberculeuse cliniquement primitive chez l'enfant de 2 à 15 ans, Rev. franç. de pédiat. **2**:604, 1926. (*b*) Beisken, W.: Aktivieren Masern die Tuberkulose? Ztschr. f. Kinderh. **40**:353, 1925. (*c*) Eckstein, A.: Beeinflussung der Tuberkulose durch andere Krankheiten, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 2, p. 1505.

develop during or shortly after an attack of whooping cough.[5] Because of this time relationship, whooping cough may appear to be the predisposing cause. However, such occurrences are uncommon [6] and may be coincidental.

A reduction in tuberculin allergy during whooping cough has been reported in a few cases.[7] A similar reduction in tuberculin allergy has been reported for many other acute infectious diseases.[8] This change, however, is most marked and most constant in measles.[9]

Significant data relative to the effects of whooping cough on tuberculosis have been obtained from studies of small groups of tuberculous children under observation before an attack of whooping cough. Several reports stressed the fact that the attack produced no ill effects on the tuberculous process.[10] Others noted activation of the tuberculous process in an occasional case only.[11] This was seen during, immediately after or months after the attack of whooping cough. There was no way of telling whether whooping cough was responsible for the change.

Numerous reasons have been presented to explain the occurrence of exacerbations during or after whooping cough. Bergeron and Bour-

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5. (*a*) Moses. F.: Der Einfluss des Keuchhustens auf die Tuberkuloseimmunität, Ztschr. f. Kinderh. **43**:398, 1927. (*b*) Goebel, F.: Die Beeinflussung der Kindertuberkulose durch hinzutretende Infektionen, Ergebn. d. inn. Med. u. Kinderh. **36**:126, 1929. (*c*) Engel, S.: Meningitis tuberkulose und Miliartuberkulose, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 1, p. 530.

6. Pospischill.[1] Meyer and Burghard.[3b]

7. (*a*) Popper, E.: Ueber Pertussis, Med. Klin. **10**:1097, 1914. (*b*) Nobécourt, P., and Forgeron, H.: La cuti-réaction à la tuberculine dans la coqueluche: l'anergie tuberculinique, Arch. de méd. d. enf. **25**:394, 1922. (*c*) Sundal, A.: Ueber Keuchhusten, Acta pædiat. **14**:104, 1932.

8. Orel, H.: Tuberkulindiagnostik, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 2, p. 904.

9. (*a*) von Pirquet, C.: Das Verhalten der kutanen Tuberkulinreaction während der Masern, Deutsche med. Wchnschr. **3**:1297, 1908. (*b*) Preisich, cited by von Pirquet.[9a] (*c*) von Gröer, F.: Allgemeine Prognostik der tuberkulösen Infektionen, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 2, p. 949.

10. Debré, R., and Cordey, F.: Etude sur l'étiologie de la tuberculose de la deuxième enfance, Rev. franç. de pédiat. **1**:158, 1925. Mouisset, F.: Coqueluche et tuberculose, Rev. de la tuberc. **7**:592, 1926. Choffé, F.: Du rôle des maladies infectieuses dans l'étiologie de la tuberculose de la deuxième enfance, Thesis, Paris, 1929. Hershey, I. J., and Ward, F.: Whooping Cough in Tuberculous Children, Am. Rev. Tuberc. **32**:612, 1935.

11. Goebel.[5b] Dumans, M.: L'influence de la coqueluche sur la tuberculose du nourrison, Thesis, Paris, 1932. Nalbant, J. P.: The Effects of Contagious Diseases on Pulmonary Tuberculosis and on the Tuberculin Reaction in Children, Am. Rev. Tuberc. **36**:773, 1937.

garel [12] found that reactivation was the rule and not the exception among children with parenchymatous lesions, whereas, no ill effects were seen among those with hilar tuberculosis. Sundal [7c] indicated that diminution in tuberculin allergy during whooping cough might be unfavorable because 1 of his patients who showed this change subsequently had exacerbation of an old pulmonary process. This influence of whooping cough and other infectious diseases, particularly measles, on tuberculin sensitiveness has been considered an important cause of tuberculous reactivation.[9a] Other factors commonly held responsible for the tuberculous changes seen during or after whooping cough are general debilitation and decrease in local pulmonary resistance.[9c] One of the important factors seems to be the aspiration of infectious material during the deep inspiration which follows the spasmodic cough. This might lead to bronchogenic dissemination in patients with open lesions.

It is often extremely difficult to determine clinically the nature of a pulmonary change during or after whooping cough, and it is even more difficult to determine its relation to the whooping cough. Formerly a frequent mistake was to diagnose tuberculosis in an emaciated child known to have whooping cough. In these cases, the clinicians were misled by the emaciation, the chronic cough, the rales in the chest and the roentgen shadows cast by the hilar, peribronchitic and pneumonic processes following whooping cough into thinking that widespread pulmonary or miliary tuberculosis had developed. This opinion was so frequently noted to be erroneous at autopsy that some investigators have adopted the view that whooping cough has no effect on the tuberculous process.[13] However, in individual cases it is reasonable to expect some unfavorable effect from a disease like whooping cough, which damages the lung tissue and debilitates the child in the cases of more severe and protracted involvement.

An outbreak of whooping cough at Sea View Hospital in the summer of 1936 afforded us the opportunity of studying the effects of whooping cough in 25 children with pulmonary or extrapulmonary tuberculosis. The disease occurred during the three months from May 15 to August 19.[14] It was characterized by a paroxysmal cough, a whoop and lymphocytosis. On the whole, the disease was mild. The average duration of the whooping stage was twenty-six days. The number of days during which the whoop was considered severe varied from zero to seventeen; the average was five.

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12. Bergeron, A., and Bourgarel: Coqueluche et tuberculose, Rev. de phtisiol. méd-soc. **8**:189, 1927.

13. Pospischill.[1] Gabriel.[3a]

14. Siegel, M., and Goldberger, E. W.: Active Immunization of Tuberculous Children Against Whooping Cough with Sauer's Vaccine, J. A. M. A. **109**:1088 (Oct. 2) 1937.

The afflicted children were isolated either at the Richmond Borough Hospital for Communicable Diseases or at the Willard Parker Hospital. The period of isolation lasted from five to six weeks. During this period 1 child died of tuberculous meningitis.

After the period of isolation 24 children returned to Sea View Hospital, where they were observed for constitutional symptoms, such as fever and loss of weight, and were followed by means of repeated physical and roentgen examinations, examinations of sputum and gastric washings for acid-fast bacilli and determinations of the erythrocytic sedimentation rate [15] and of the intracutaneous reaction to tuberculin.

The period of observation extended through Dec. 31, 1937. Twenty-one children were observed after whooping cough for sixteen to nineteen months, while 3 were observed for two, six and nine months, respectively.

The age distribution at the time whooping cough occurred was as follows:

| Age in Years | No. of Children |
|---|---|
| 1 | 2 |
| 2 | 5 |
| 3 | 7 |
| 4 | 7 |
| 5 | 3 |
| 7 | 1 |

The average age was about 3½ years. There were 19 boys and 6 girls. Four children were white, and the others were Puerto Ricans or Negroes born in the United States.

The clinical forms of tuberculosis were distributed as follows:

| Type of Tuberculosis | State of Activity | No. of Cases |
|---|---|---|
| Primary pulmonary | Active | 15 |
| | Inactive | 1 |
| Hilar lymph node | Active | 2 |
| | Inactive | 3 |
| Disseminated pulmonary | Active | 2 |
| Generalized miliary | Active | 1 |
| Upper thoracic vertebral | Active | 1 |

A cavity could be distinctly seen in 1 case only. Acid-fast bacilli were detected in 7 cases by direct microscopic examination of stained smears. The sedimentation rate of the red blood cells was abnormally high in 15 children. There were constitutional symptoms in 7 children. All the children had positive reactions to doses of 0.01 mg. of old tuberculin.

The average stay at Sea View Hospital prior to the onset of whooping cough was eleven months. Eight children were hospitalized for

15. A modification of Cutler's method, using the Westergren tube, was employed.

less than six months, 9 children from six months to a year and 8 children from one to three years. During this period, the course of the tuberculous process was retrogressive in 20 children. Reactivation or dissemination occurred in 5 children. This was transient in 2 children, appearing as recurring phlyctenular keratoconjunctivitis in one and as contralateral tuberculous pleural effusion in the other. The tuberculous changes were progressive in the 3 other children, leading to miliary tuberculosis in 1, to slow extension of an upper thoracic type of Pott's disease in another and to the development of a tuberculous focus in the metaphysis of the tibia in the third.

## RESULTS

1. During the period of isolation 1 infant contracted tuberculous meningitis; the child died four weeks after the onset of the whoop.

CASE 1.—J. P., a Puerto Rican boy, was admitted to Sea View Hospital in March 1936, at the age of 8 months, as a tuberculous contact with a negative intracutaneous reaction to 10 mg. of old tuberculin. Clinical signs of pulmonary tuberculosis developed in April, and roentgen evidence of miliary pulmonary tuberculosis appeared in June, a month prior to the onset of whooping cough. The child was isolated on July 28, when the whoop was first heard. At that time the white blood count reached 60,400 per cubic millimeter, with 63 per cent lymphocytes. Listlessness and apathy were noted on August 3. Generalized convulsions occurred on August 12, when rigidity of the neck and spasticity of the extremities were first observed. The child died on August 25. Postmortem examination revealed caseating primary tuberculosis, generalized miliary tuberculosis, tuberculous enterocolitis and tuberculous leptomeningitis.

The tuberculous meningitis developed during the paroxysmal stage of whooping cough in an infant with rapidly progressing primary pulmonary and miliary tuberculosis. Because of this time relationship, whooping cough may appear to have been the predisposing cause of the tuberculous meningitis. It is impossible to decide definitely whether this is so. It is known, however, that tuberculous meningitis occurs in infants who have progressing primary and miliary tuberculosis, without a past history of whooping cough in most instances.[16]

Four children were tested intracutaneously with tuberculin during the period of isolation at Willard Parker Hospital. The reactions to doses of 0.01 mg. of old tuberculin were reported as varying in diameter from 20 to 50 mm. There was formation of vesicles in 1 case. The tests were performed once, during the first week of the whooping stage, when the temperature was below 100 F. by rectum.

2. Examinations after the period of isolation revealed no discernible ill effects in 18 children and unfavorable changes in 6. These unfavorable changes were seen either immediately after the child's return from

16. Debré and Cremieu-Alcan.[4a] Eckstein.[4c] Engel.[5c]

the isolation hospital or from two to four months later. Two of the 6 children had progressing extrapulmonary foci prior to the onset of whooping cough; these continued to progress after the attack. Four children had evidence of pulmonary changes, which were interpreted as tuberculous in 2 and as nontuberculous in the other 2.

*A.* Of the 2 children with progressive extrapulmonary foci, one child had a tuberculous focus in the metaphysis of the tibia and retrogressing primary pulmonary tuberculosis; the other child had tuberculosis of the first, second, and third thoracic vertebrae with no detectable pulmonary lesions. The children were 24 and 21 months old, respectively, when whooping cough developed.

CASE 2.—A. G., a Negro boy, was admitted to Sea View Hospital in November 1935, at the age of 16 months, with active primary pulmonary tuberculosis in the upper lobe of the right lung. One gastric washing, made in November 1935, was positive for acid-fast bacilli on direct examination of a smear. None of the others contained the organisms. By March 1936 there was considerable retrogression of the primary process. In May 1936, two months prior to the onset of whooping cough, a tuberculous focus developed in the metaphysis of the tibia. The sedimentation rate at this time was 22 mm. in forty-five minutes. The extrapulmonary lesion progressed steadily. Whooping cough was diagnosed on July 17. The whoop lasted twenty-seven days and was severe for eleven days. The child returned from the isolation hospital on September 2 with no constitutional symptoms, no unfavorable pulmonary effects and no change in the sedimentation rate. The tuberculous focus in the tibia continued its progression during and after the period of isolation. However, there seemed to be no increase in the rate of progression. In the meantime, the pulmonary lesion was undergoing fibrosis and calcification. In April 1937 the sedimentation rate had fallen to 11 mm. in forty-five minutes; it remained at this level.

CASE 3.—J. B., a Negro boy, was admitted to Sea View Hospital in May 1936, at the age of 19 months, with tuberculosis of the first, second and third thoracic vertebrae and no detectable pulmonary lesions. There was no perceptible change prior to the onset of whooping cough, which was diagnosed on July 19. The whoop lasted eighteen days and was severe for four days. The child returned from the isolation hospital on August 26 with no constitutional symptoms, no detectable pulmonary lesions and no apparent change in the status of Pott's disease. The intracutaneous reaction to 0.01 mg. of old tuberculin remained about the same: It measured 15 mm. on May 19, before whooping cough, and 12 mm. on August 27, after whooping cough. The sedimentation rate fell from 40 mm. on May 20 to 7 mm. on August 27. It remained at this low level until Aug. 19, 1937, when it rose to 15 mm. in forty-five minutes. Extremely slow progression of the Pott's disease was noticeable after periods of three to six months. In July, a year after the attack of whooping cough, there was extensive destruction of the upper thoracic vertebrae (first to fourth dorsal).

In neither of these patients with extrapulmonary tuberculosis were there discernible differences in the rates of progression of the extrapulmonary foci before and after whooping cough, indications of a change in tuberculous activity as a consequence of the whooping cough or

unfavorable pulmonary effects. Therefore, there is no evidence that the attack of whooping cough had harmful effects in these cases.

*B.* Of the 2 children with nonspecific pulmonary changes, 1 child had roentgen evidence of chronic pneumonitis in the lower lobe of the right lung immediately on his return from the isolation hospital; the other child contracted acute fatal "bronchopneumonia" two months after the attack of whooping cough.

CASE 4.—J. S., a Puerto Rican girl, was admitted to Sea View Hospital in January 1936, at the age of 3½ years, with an active primary lesion in the apex of the lower lobe of the right lung and large regional hilar nodes containing several calcified deposits. The primary pulmonary complex retrogressed considerably without any evidence of exacerbation during the six months prior to the onset of whooping cough. Acid-fast bacilli were detected on direct microscopic examination of stained smears made of a concentrated gastric washing in March; numerous other examinations gave negative results. The sedimentation rate in January was 4 mm. and in May was 3 mm. in forty-five minutes. Whooping cough was diagnosed on July 14. The whoop lasted thirty days and was severe for ten days. The child was isolated until August 27, when she was returned to Sea View Hospital with no constitutional symptoms and no abnormal clinical signs. The sedimentation rate was 5 mm. in forty-five minutes on August 28 and 3 mm. on November 5. No acid-fast bacill were detected by direct examination of smears of sputum and of gastric washings. There was no change in the intracutaneous reaction to 0.01 mg. of old tuberculin. The reaction (induration) measured 15 mm. in diameter in June, one month before whooping cough, and 15 by 12 mm. in August, after whooping cough. The only detectable change was that seen in the roentgenogram taken on August 28, a day after the child returned from the isolation hospital. The bronchovascular markings in the medial zone of the lower part of the right pulmonary field were moderately increased, particularly in the medial portion of the base. The right hilar shadow was slightly increased. These changes persisted for two months before a decrease in the density of the shadows was seen. Up to the time of writing there have been no recurrences. The last roentgenogram was taken in December 1937.

The roentgen changes observed in the hilus and in the lower lobe of the right lung immediately after the child's return from the isolation hospital are compatible with chronic pneumonitis. These changes may have been either tuberculous or nontuberculous. They occurred without evidence of an increase in tuberculous activity and were therefore interpreted as nonspecific inflammatory changes similar to those occasionally seen in nontuberculous children during the course of whooping cough.

CASE 5.—A. F., a feebleminded (microcephalic) white boy, was admitted to Sea View Hospital in March 1934, at the age of 2 years, with active primary pulmonary tuberculosis in the upper lobe of the left lung. No acid-fast bacilli were detected in the sputum or gastric washings by direct examination of stained smears. The disease regressed steadily without evidence of exacerbations, and by June 1936, a month prior to the onset of whooping cough, there were extensive fibrotic changes in the left perihilar region and large calcified deposits in the hilar

regions. The sedimentation rate was 11 mm. in forty-five minutes. Whooping cough was diagnosed on July 28. The child whooped for twenty-four days, and the whooping seizures were severe for two days. He returned from the isolation hospital on August 28, showing no change in his tuberculous condition. He was afebrile; there were no abnormal physical signs; the sedimentation rate was 10 mm. in forty-five minutes; the sputum and gastric washings contained no tubercle bacilli, and the roentgen findings were similar to those seen before whooping cough occurred. On October 20 the patient, apparently in good health, was transferred to a state institution for the feebleminded. According to the records at the institution, the child contracted an acute infection of the upper respiratory tract a few days after he entered the institution. This rapidly progressed to bronchopneumonia, which was fatal on November 7, eighteen days after the patient's admission to the institution. Permission for postmortem examination was not granted. There were no roentgen studies of the chest or examinations of the sputum for acid-fast bacilli.

The acute fatal pulmonary infection developed two months after the attack of whooping cough in a child with a fibrotic calcifying primary lesion. No apparent ill effects following the whooping cough were noticed during the period of observation at Sea View Hospital. The acute infection of the upper respiratory tract, which developed two months later, soon after admission to another institution, and was followed in a few days by rapidly fatal acute bronchopneumonia, appears to have been unrelated to the whooping cough and the tuberculosis.

*C.* In the 2 children with specific pulmonary changes, exacerbations of primary pulmonary lesions appeared four months after the attack of whooping cough.

Case 6.—J. N., a Puerto Rican boy, was admitted to Sea View Hospital in September 1935, at the age of 26 months, with congenital syphilis and an active primary lesion in the middle lobe of the right lung with extensive postprimary involvement in this region. The tuberculous process retrogressed considerably without any evidence of exacerbation during the ten months of hospitalization prior to the onset of whooping cough. Smears of the sputum and of the gastric washings contained no acid-fast micro-organisms on direct examination. The sedimentation rate in June 1936, a month before the attack of whooping cough, was 7 mm. in forty-five minutes. The congenital syphilis was treated with acetarsone from November 1935 to June 1936; the Wassermann reaction was negative on June 30, 1936. Whooping cough was diagnosed on July 31. The whoop lasted twenty-nine days and was severe for three days. The child was isolated until August 22, when he was returned to Sea View Hospital with no fever or abnormal physical signs. Sedimentation rate was 10 mm. in forty-five minutes on August 22 and 8 mm. in September and November. The Mantoux reaction to 0.01 mg. of tuberculin measured 3 mm. in June, before whooping cough, and 6 mm. on August 30, after whooping cough. The roentgen findings on August 24 were similar to those seen in the roentgenogram taken on July 1, shortly before whooping cough was diagnosed. No appreciable change was noticed until December 30, four months later, when an increase in the extent and density of the shadow in the lower part of the right pulmonary field was seen. This was interpreted as an exacerbation of the primary lesion in the middle lobe of the

right lung. There was no fever; the sedimentation rate was 9 mm. in forty-five minutes, and there were no abnormal physical signs. The subsequent course was benign. The roentgen shadow persisted with little or no change until June 1937, when some clearing was noticed. Improvement continued without exacerbations. Direct examination of smears of sputum and of gastric washings gave negative results. Only one gastric washing was cultured. This was done on June 9, 1937; it showed the presence of tubercle bacilli. The sedimentation rate in July 1937 was 2 mm. in forty-five minutes; in February 1938 it was 7 mm.

Exacerbation of a regressing primary pulmonary lesion occurred four months after an attack of whooping cough. In view of the absence of clinical evidence of an increase in tuberculous activity until the fourth month after the attack, it seems difficult to attribute the exacerbation to the whooping cough, although this possibility cannot be ruled out entirely.

CASE 7.—E. R., a Negro boy, was admitted to Sea View Hospital in May 1936, at the age of 11 months. He had an active primary lesion in the lower lobe of the right lung, with very large regional hilar nodes. The liver extended to the level of the navel. In the right lower quadrant were irregular masses which were thought to be ileocecal nodes; the spleen was not palpable. No acid-fast bacilli were observed on direct examination of smears of the sputum and gastric washings. The sedimentation rate was 16 mm. in forty-five minutes. There was a low grade fever, the temperature frequently reaching 101 F. Whooping cough was diagnosed on July 18, two months after the patient's admission. The whoop lasted thirty-three days and was severe for four days. The child returned from the isolation hospital on August 26 with bilateral purulent otitis media, a profuse purulent nasal discharge and extensive pyoderma. There were no detectable pulmonary changes. The pyogenic infection lasted two weeks. The temperature reached a normal level after September 3. It remained normal until November 28, when it suddenly rose to 104 F. with the development of acute follicular tonsillitis. Bilateral purulent otitis media developed within forty-eight hours. The temperature was 103 to 104 F. for six days before it began to fall. On December 5, seven days after the onset of this acute episode, rales were audible for the first time in the lower lobe of the right lung, and an increase in the extent and density of the shadow in this lobe was noticed. These changes were attributed to exacerbation of the tuberculous process in this region. No tubercle bacilli were noted on direct examination of smears of the sputum and gastric washings. In January, about a month after the pulmonary exacerbation, progressive enlargement of the cervical nodes was noticed. These reached massive size on the left. Softening and spontaneous discharge of cheesy purulent material occurred in February, persisted for four weeks and was followed by slow spontaneous healing within two months. The roentgen shadows indicative of tuberculous exacerbation remained unchanged for four months. At the end of six months there was slight regression, and after nine months there was considerable resolution.

Exacerbation of an active primary pulmonary lesion occurred in a cachectic infant with extensive lymphadenopathy four months after the attack of whooping cough. There had been no evidence of increased tuberculous activity prior to this. Furthermore, a virulent pyogenic infection of the tonsils and middle ears immediately preceded the exacer-

bation. In view of these facts, there seems to be little, if any, causal relation between the tuberculous exacerbation and the antecedent whooping cough.

*D.* As for the 18 children with no discernible ill effects, at no time during the entire period of observation after whooping cough did they show any evidence of exacerbation of the tuberculosis. In case the disease was retrogressing before the onset of whooping cough, it continued uninterruptedly in the same direction after the attack, as if whooping cough had never occurred. If the process was apparently quiescent, it continued to be so, as far as we could tell by the methods employed in the investigation.

The clinical forms of tuberculosis in these 18 children are shown in the tabulation.

| Type of Tuberculosis | State of Activity | No. of Cases |
|---|---|---|
| Primary pulmonary | Active | 10 |
| | Inactive | 1 |
| Hilar lymph node | Active | 2 |
| | Inactive | 3 |
| Disseminated pulmonary | Active | 2 |

One child had an extensive primary and postprimary involvement of the upper lobe of the left lung with a cavity 1½ inches (3.8 cm.) in diameter and disseminated lesions throughout both lungs. Considerable atelectasis and retraction of the upper lobe of the left lung had occurred before the attack of whooping cough. Retraction and fibrosis continued after the attack, which seemed to have no unfavorable effects.

Acid-fast bacilli were detected in the sputum or gastric washings of 5 children by direct microscopic examination of stained smears. Only 2 of these children continued to have positive smears after whooping cough. The erythrocytic sedimentation rates of 10 children were abnormally high before the attacks of whooping cough. After the attacks the rates were reduced for all 10 children, remaining above normal levels in only 4 cases.

## SUMMARY

The effects of whooping cough on tuberculosis were studied in 25 children with pulmonary and extrapulmonary tuberculosis. The average duration of observation after the attack of whooping cough was sixteen months.

During the attack of whooping cough, 1 child with miliary tuberculosis contracted tuberculous meningitis. We had no way of telling whether the attack of whooping cough was instrumental in bringing about the tuberculous meningitis or was merely coincidental.

After the attack of whooping cough, specific changes were noted in 2 children. In both, exacerbations of primary pulmonary lesions devel-

oped four months after the attack. There was no evidence to indicate that the exacerbations were caused by the whooping cough.

In the remaining 22 children, there was no increase in tuberculous activity. The tuberculous process retrogressed or remained quiescent in 20 children and progressed slowly, without apparent increase in rate, in 2 children with extrapulmonary foci.

## CONCLUSIONS

With 1 possible exception, whooping cough seemed to have no specific effect on tuberculosis in the 25 children studied by us. However, the small number of children observed and the mildness of the disease in most cases do not permit us to make the definite statement that whooping cough has no effect on an active tuberculous process in the lungs. It is reasonable to assume that a focus in the lung in open communication with the air passages may spread by the bronchogenic route under the effect of the convulsive attacks of coughing which raise the infected exudate and secretions to a higher level along the bronchial tree. The infectious material may then be carried to healthy parts of the lung by the deep inspiration which follows the attack of coughing. This danger connected with whooping cough may be more important than other factors which are frequently mentioned in the literature, such as the lowering of tuberculin sensitiveness. Completely arrested tuberculosis will probably not be aggravated by the occurrence of whooping cough. This also seems to be true of extrapulmonary foci, except those mechanically affected during the paroxysms.

# HYPOTHYROIDISM AND CRETINISM IN CHILDHOOD

## VI. INFLUENCE OF THYROID THERAPY ON MENTAL GROWTH

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It is generally known that untreated congenital thyroid deficiency [1] is characterized by lack of statural growth and by marked retardation of dentition, sitting, walking and talking. Mental development is extremely slow, and there are sluggishness and absence of emotional response. Metabolism is markedly reduced; body temperature may be subnormal, and the appearance of carpal development is greatly delayed.

In 1934 we published a preliminary report [2] on the influence of thyroid therapy on the mental development of a group of 21 children, 2 who had juvenile hypothyroidism and 19 cretins. At that time the following tentative conclusions were reached: 1. There is evidence that early recognition of the affliction and persistent treatment thereafter are the important factors in ultimate mental development. 2. Not all cretins, if treated, are predestined to a fixed low mental age. Some of them may reach a mental age of at least 12 years. 3. Most of these children have intelligence ratings between 50 and 70, and if treated they will probably have at maturity a mental age between 8 and 10 years.[3] 4. Some cretins continue to show growth up to the age of 14 years. 5. The children who have normal birth and developmental histories but

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1. In this paper the terms "cretin," "thyroid deficiency" and "hypothyroidism" will be used interchangeably. The term "juvenile hypothyroidism" will be applied to those children in whom the thyroid gland was normal at birth but the function was later disturbed by some disease of childhood. For discussion of the nomenclature regarding hypothyroidism, see Bronstein, I. P., and Milles, G.: Hypothyroidism and Cretinism in Childhood: IV. Postmortem Reports on Two Cretins, Am. J. Dis. Child. **49**:1564 (June) 1935.

2. Bronstein, I. P., and Brown, A. W.: Hypothyroidism and Cretinism in Childhood: III. Mental Development, Am. J. Orthopsychiat. **4**:413 (July) 1934.

3. In our preliminary report the mental age at maturity was given as 7 to 9 years. The mental ratings just cited are consistent with the intelligence quotient.

who have thyroid deficiency later in life after a specific or a series of nonspecific infections (juvenile hypothyroidism) progress successfully if properly treated.

In 1936 Gesell,[4] in a study of 6 cretin girls, stated: "The mental status under treatment varied widely from persisting severe mental deficiency to normal intelligence." Recently a study of cretinism in London was reported by Lewis.[5] The investigation was especially concerned with the psychologic effects of thyroid deficiency and the benefit of thyroid therapy on the mental development.

This paper is the result of continued observation of the cases reported earlier as well as of additional cases which have accumulated since that time.

These children have been given psychologic examinations yearly since the time they were first brought to the hospital. For children of mental ages below 3 years, the Kuhlmann-Binet, the Merrill-Palmer or the Minnesota preschool test was used; for children above a mental age of 3 years the 1916 revision of the Stanford-Binet test was used. The Goodenough drawing test and a series of performance and achievement tests were given to a number of the children. The thyroid treatment has been active and persistent and perhaps as well controlled as is possible under the circumstances since referral to our care. In a number of instances treatment was initiated before the child came to the clinic, and in such a case there is no accurate record of the previous therapy; we have therefore had to rely on the report of the parents or the memory of the physician who treated the child. It is possible that some of these records may be inaccurate; this may account for some of the inconsistencies in the data.

The data from which conclusions are drawn are based on the results of the examination of 29 children, 17 girls and 12 boys. In so small a number the preponderance of girls may be due to chance. This incidence, however, is in agreement with that of other studies.[4] The essential data regarding these cases are presented in table 1.

In general the children were severely retarded mentally even after periods of persistent treatment lasting from 1 to 7 years, the average (median) intelligence quotient of the group being 61. In 75 per cent of the cases the intelligence quotient was below 80, and in 25 per cent, below 45, i.e., at the imbecile level or below, while in 2 cases the quotient was above 100. In both of these cases it was reported that the treatment was started early. In 1 case the record stated that treatment began at the age of 6 weeks and had been regular since; in the other it was reported that the treatment had been active and persistent since the age of 19 months. There is some evidence, therefore, that the best results

4. Gesell, A.; Amatruda, C. S., and Culotta, C. S.: The Effect of Thyroid Therapy on the Mental and Physical Growth of Cretinous Infants, Am. J. Dis. Child. **52**:1117 (Nov.) 1936.

5. Lewis, A.: Study of Cretinism in London, Lancet **1**:1505 (June 26) 1937; **2**:5 (July 3) 1937.

TABLE 1.—*Successive Intelligence Quotients Determined Since Referral to the Clinic**

TABLE 1.—*Successive Intelligence Quotients Determined Since Referral to the Clinic* *

| Subject | Sex | Age at Time of First Test | | Successive Intelligence Quotients | | | | | | Period of Active Treatment Since First Test | | Amount of Change in Intelligence Quotient Since First Test | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Yr. | Mo. | 1st | 2d | 3d | 4th | 5th | 6th | Yr. | Mo. | | |
| A. B. | M | 11 | 9 | 48 | 38 | 41 | 38 | 41 | 42 | 6 | 11 | — 6 | Irregular from 2 to 8 yr., none from 8 yr. to 11 yr. 9 mo., regular since |
| M. B. | F | 8 | 1 | 72 | 77 | .. | ... | ... | .. | 1 | 3 | + 5 | Began at 11 mo., continuous until 7 yr., discontinued for 1 yr., continuous since 8 yr. |
| L. B. | F | 6 | 1 | 107 | 102 | 96 | 100 | 111 | .. | 3 | 10 | + 4 | Active since 11 mo. |
| M. B. | M | 12 | 3 | 20 | 20 | .. | ... | ... | .. | 1 | 1 | No observable change | No record of treatment before referral |
| K. B. | F | 3 | 11 | ? | 50? MP | 56 | 55 | 53 | .. | 3 | 7 | + 3 | Began at 3½ yr., irregular to first examination, regular since |
| D. B. | F | 1 | 2 | ? | ? | 77 | ... | ... | .. | 2 | 1 | ? | Began at 4 mo., regular since |
| B. C. | F | 1 | 1 | ? | 45? KB | 35? KB | 35? KB | Committed 8/29/36 | | 2 | 10 | ? | Began at 14 mo., regular to time of commitment |
| J. C. | M | 6 | 10 | 51 | 43 | 41 | 51 | 57 | 46 | 5 | 6 | — 5 | Irregular to 7 yr., regular since |
| R. C. | F | 7 | 10 | 49 | 46 | 48 | 50 | 53 | .. | 5 | 7 | + 4 | Irregular and uncertain since recognition at 1 yr. |
| J. D. | M | 0 | 6 | 80? | ... | .. | ... | ... | .. | .. | .. | .... | Began at 6 mo. |
| J. F. | M | 10 | 0 | 43 | 48 | 54 | 54 | 52 | 53 | 5 | 5 | +10 | Irregular to time of first examination, regular since |
| A. G. | M | 16 | 1 | 81 | 80 | 83 | 85 | ... | .. | 5 | 10 | + 4 | Little and irregular before 8 yr., regular since, very active last 6 yr. |
| L. H. | F | 12 | 0 | Idiot level | ... | .. | ... | ... | .. | Seen once | | .... | None reported before referral |
| L. H. | M | 6 | 0 | 69 | 70 | 66 | 74 | 67 | .. | 3 | 9 | — 2 | Began at 12 mo., off treatment from 5th to 6th yr., active since 6 yr. |
| T. I. | F | 8 | 1 | 76 | 61 | 67 | ... | ... | .. | 2 | 1 | — 9 | Began at 8 yr., regular since |
| D. J. | F | 5 | 5 | 62 | 67 | 68 | 73 | 71 | 77 | 3 | 8 | +15 | Began at 1 yr., irregular until 5 yr., regular since |
| O. K. | M | 11 | 8 | 74 | 73 | 72 | 69 | 83 | .. | 5 | 6 | + 9 | Began at 2 yr., irregular throughout |
| A. K. | F | 11 | 7 | 60 | 50 | 51 | 56 | 62 | .. | 5 | 0 | + 2 | No record of treatment before 11 yr. |
| V. K. | F | 11 | 10 | 54 | 58 | 58 | 54 | 54 | .. | 3 | 9 | 0 | Fairly good since about 2 yr., active since first examination |
| D. M. | F | 0 | 7 | ? | ? | 82? KB | ... | ... | .. | 1 | 0 | .... | Began at 6 mo., active since |
| G. M. | M | 8 | 10 | 53 | 62 | 58 | 64 | 70 | 71 | 5 | 0 | +18 | Began at 2 yr., active since referral |
| R. P. | F | 4 | 11 | ? | 38? | 35? | 32? | 29? KB | .. | 4 | 11 | ? | Began at 5 yr., active since referral |
| C. R. | M | 8 | 0 | 42 | 38 | 40 | ... | ... | .. | 1 | 11 | — 2 | Began at 7 mo., irregular for 6 yr., active since referral |
| F. S. | F | 7 | 6 | 96 | 96 | 108 | ... | ... | .. | 1 | 10 | +12 | Began at 6 wk., regular since |
| E. S. | F | 13 | 3 | 33? | 35 | .. | ... | ... | .. | 1 | 3 | ? | No record before referral, active since |
| J. S. | M | 3 | 4 | 55? MP | 60? | 61 | 54 | 63 | 72 | 4 | 9 | ? | Began at 2 yr., active since referral |
| J. S. | F | 9 | 8 | 53 | 46 | 47 | 49 | 44 | .. | 3 | 8 | — 9 | Began at 3 yr., active since referral |
| D. V. | M | 1 | 3 | ? | ? | 76? MP | ... | ... | .. | 1 | 7 | .... | Began at 3 mo., active since referral |
| M. Y. | F | 10 | 8 | ? | ? | 40 GD | ... | ... | .. | 1 | 9 | .... | No record before referral |
| L. C. | F | 16 | 4 | 86 | 84 | 86 OSA | ... | ... | .. | 1 | 7 | Juvenile hypothyroidism | Hypothyroidism developed at 15 yr., adequate treatment since |
| G. L. | F | 3 | 1 | 59 MP | 84 | 94 | ... | ... | .. | 2 | 1 | Juvenile hypothyroidism | At 1½ yr. pertussis developed after which hypothyroidism appeared; active treatment since |
| H. P. | F | 13 | 0 | 104 | 93 | .. | ... | ... | .. | 1 | 10 | Juvenile hypothyroidism | Hypothyroidism developed at 10 yr., active treatment since |
| M. R. | F | 7 | 8 | 89 | 100 | .. | ... | ... | .. | 1 | 3 | Juvenile hypothyroidism | Hypothyroidism developed at 3 yr., active treatment since |

* MP indicates Merrill-Palmer test; GD, Goodenough drawing test; OSA, Otis self-administering test, and KB, Kuhlmann-Binet test.

are obtained in the cases in which an early diagnosis is made and in which persistent and active treatment is carried on thereafter.

Although 25 per cent of the subjects were at the imbecile level and 50 per cent at the borderline or high grade defective level in spite of persistent and active treatment, it should be recognized that without treatment all of them would probably be at the imbecile or idiot level.

Table 2 shows the relation between the age at which treatment began and the level of intelligence after the period of treatment. The period of active treatment after referral to the clinic ranged from one to seven years. The average chronologic age at the time of the last test was 10.9 years.

It is clear from an inspection of the table that there is some relation between the age at which treatment began and the level of mental devel-

TABLE 2.—*Relation Between Mental Development and Age at Which Treatment Began* *

| Level of Development† | Age at Which Treatment Began, Yr. | | | | | | | Number of Cases |
|---|---|---|---|---|---|---|---|---|
| | 0-2 | 2-4 | 4-6 | 6-8 | 8-10 | 10-12 | 12-14 | |
| 110-119 | 1 | .. | .. | .. | .. | .. | .. | 1 |
| 100-109 | 1 | .. | .. | .. | .. | .. | .. | 1 |
| 90-99 | .. | .. | .. | .. | .. | .. | .. | 0 |
| 80-89 | 2 | 1 | .. | .. | 1 | .. | .. | 4 |
| 70-79 | 5 | 1 | .. | .. | .. | .. | .. | 6 |
| 60-69 | 1 | .. | .. | .. | 1 | 1 | .. | 3 |
| 50-59 | 1 | 2 | .. | .. | 1 | .. | .. | 4 |
| 40-49 | .. | 2 | .. | 1 | .. | 2 | .. | 5 |
| 30-39 | 1 | .. | .. | .. | .. | .. | 1 | 2 |
| 20-29 | .. | .. | 1 | .. | .. | .. | 1 | 2 |
| 10-19 | .... | | .. | .. | .. | .. | 1 | 1 |
| Total | | | | | | | | 29 |

* Intelligence quotient according to the most recent test.
† Median I. Q. = 61.0; $Q_1$ = 44.5; $Q_2$ = 77.9.

opment. With 1 exception all subjects with an intelligence quotient above 70 began treatment before the age of 4 years. On the other hand, some of those who began treatment at an early age remained extremely retarded. In the first column, which shows the distribution of cases in which treatment was started before the age of 2 years, there is a range in intelligence quotient from 35 to 105.

The question immediately arises: Why are some children so much more responsive to treatment than others? Several possibilities suggest themselves. 1. The treatment before referral may not have been as active and persistent for those with the low ratings as for those with the higher ratings. 2. The glandular dysfunction may have been more severe in those who remained at the lower level than in those at the higher level; i.e., the hypothyroidism in these sporadic cretins may be a matter of degree. 3. In some cases the failure to develop may be due to the fact that the thyroid deficiency was associated with or simply imposed on primary feeblemindedness. It is more than probable that this

was so in the last case in the first column of table 2. The father was found to be feebleminded by the court psychologist, and at the time of writing the mother is an inmate of a state hospital for the insane. Therefore, any one of a number of factors may account for the failure of some children to respond to thyroid treatment.

Tredgold [6] has advanced the suggestion that the failure of some cretins to improve under thyroid treatment may be explained by postulating two types of cretinism: one in which both the mental and the physical retardation are clearly due to the hypothyroidism and one in which the retardation is due to primary amentia. There is no evidence in our data to support this hypothesis. While it is true that primary amentia may prevent development even though treatment is started very

TABLE 3.—*Relation Between Mental Ratings of Cretins After Treatment and Mental Ratings of Their Siblings*

| Patient | Latest Intelligence Quotient of Patient | Intelligence Quotient of Patient's Siblings | Difference in Intelligence Quotient |
|---|---|---|---|
| M. B. | 77 | 108 | 31 |
| D. J. | 77 | 136 | 59 |
| D. V. | 76 | 102 | 26 |
| J. Si. | 72 | (1) 101 | 29 |
| | | (2) 98 | 26 |
| G. M. | 71 | 109 | 38 |
| T. L. | 67 | (1) 90 | 23 |
| | | (2) 82 | 15 |
| V. K. | 54 | 78 | 24 |
| J. F. | 53 | 94 | 41 |
| J. St. | 44 | 98 | 54 |
| C. R. | 40 | 79 | 39 |
| E. S. | 35 | 88 | 53 |
| Average | 60.5 | 97.1 | 35.2 |

early, there are a number of cretins who fail to respond to treatment, even though it is initiated at an early age, and in whom there is no primary amentia so far as can be determined from the social history.

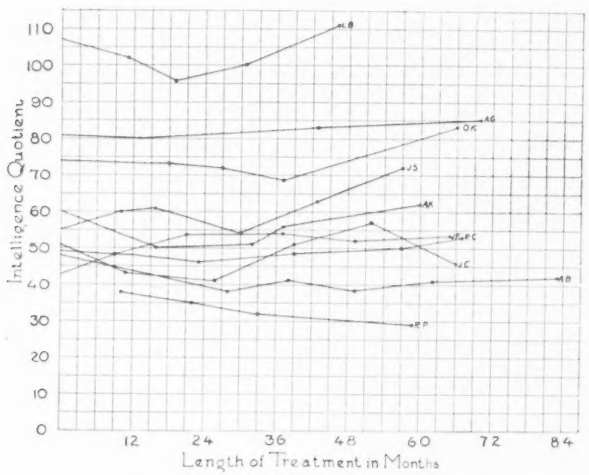
Stanford-Binet ratings were secured for 13 siblings of 11 cretins. These are shown in table 3. The average intelligence quotient of the cretins was 60.5, while the average quotient of their siblings was 97.1, with a range from 78 to 136. Although the number of cases is small, there is nothing to indicate that cretinism is confined to families of low intellectual or low social status.

It is interesting to note the relation between the mental development and the ossification of the carpal bone. Roentgenograms of the wrists of 13 children were secured before active treatment was begun. The ages of these children averaged 8 years and 5 months; the range was from 3

6. Tredgold, A. F.: Mental Deficiency, New York, William Wood & Company, 1929, p. 274.

years and 1 month to 16 years and 4 months. The mental ages of the group averaged 4 years and 7 months, ranging from 2 years to 12 years and 10 months. The approximate age levels of the carpal development averaged 5 years and 4 months, ranging from 2 to 13 years. While the number of cases is too small for any definite conclusions, there is evidence of some relation between mental and carpal development.

The chart shows the intelligence quotients of those patients who had treatment for four years or more. The quotients, which were obtained on successive examinations during the period of treatment were low in comparison with those of average children. While there were fluctuations, they were not great, and they occurred in both directions. In gen-




The level of intelligence at each examination during the period of treatment since referral to the clinic.

eral, during the period of treatment after referral to the clinic the ratings tended to increase slightly.

The average fluctuation of 6 points for the entire group is only slightly greater than that for normal children. The fluctuation ranged from —9 to +18, with a mean algebraic change of +2.7.

Twenty-two of the children were given a variety of performance and achievement tests. There seems to be no evidence from the data that cretins have any special aptitudes or abilities. The retardation is general. The average rating on the Goodenough drawing a man test was 70, including a rating of 136 made by a cretin who had had a large amount of special practice in just this type of drawing in his special class. On the performance tests the children invariably ranked lower than on the Stanford-Binet tests.

## CONCLUSIONS

In this study of 29 cretins and 4 "juvenile hypothyroid" children who were being actively treated with thyroid were given psychologic tests over a period of from one to seven years to determine by quantitative measurement both the amount and nature of their mental development.

Continued observations, as reported in this study, supported the following conclusions:

1. Cretins if treated are not all predestined to a fixed low mental age. A small proportion of them may develop normally.

2. There is evidence that early recognition of the abnormal condition and active and persistent treatment thereafter are the important factors in producing ultimate mental development.

There are a number of factors which may account for the failure of some children to respond to treatment even though it is initiated early.

In general, there was a slight increase in the intelligence quotient during the period of treatment since referral to the clinic. The increase was greatest for those who began treatment early.

Even with treatment, most of the children remained severely retarded, having intelligence quotients below 70. The chances are that at maturity their mental level will not be much above 10 or 11 years.

There is no evidence from our data that cretins have any special aptitudes or abilities. The retardation seemed general.

When on successive examinations mental ages were plotted in Heinis mental growth units, the curves seemed to have the same general shape as the curve for the average child except that they were at a lower level.

Examination of a number of the siblings indicated that the cretins did not come from families of low intellectual status.

In a study of 13 cretins there appeared to be some relation between development of carpal bones and mental age.

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# IMMUNOLOGIC RESPONSE TO INGESTION OF FOODS BY NORMAL AND BY ECZEMATOUS INFANTS

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The introduction of cow's milk into the diet of normal infants results in absorption of cow's milk protein in amounts sufficient to be detected in the circulating blood by complement fixation.[1] The antigenic protein which is absorbed may stimulate the production of specific antibodies, demonstrable by precipitation and complement fixation or by cutaneous hypersensitiveness.[2] Despite continued ingestion of the protein, precipitins and cutaneous hypersensitiveness are present for only a short time; but complement fixation antibodies may remain for several months. After the initial ingestion of large amounts of crystalline egg albumin, sheep serum and almond, precipitins and cutaneous hypersensitiveness are also demonstrable. These reactions occur with such frequency after the introduction of protein foods that the absorption of unaltered protein and the subsequent development of an immune response may be considered physiologic.

Furthermore, Anderson and Schloss[3] and others have shown that the permeability of the gastrointestinal tract is increased in infants with nutritional disorders and that transient cutaneous hypersensitiveness, precipitins and passive transfer antibodies may be detected during convalescence.

It seemed possible that the immune response to initial ingestion of foreign proteins might differ in persons in whom clinical manifestations

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1. Lippard, V. W.; Schloss, O. M., and Johnson, P. A.: Immune Reactions Induced in Infants by Intestinal Absorption of Incompletely Digested Cow's Milk Protein, Am. J. Dis. Child. **51**:562 (March) 1936. (The earlier literature on intestinal absorption of antigenic proteins is cited in this report.)

2. (*a*) Lippard and others.[1] (*b*) Anderson, A. F.; Schloss, O. M., and Myers, C.: The Intestinal Absorption of Antigenic Protein, Proc. Soc. Exper. Biol. & Med. **23**:180, 1925. (*c*) DuBois, R. O.; Schloss, O. M., and Anderson, A. F.: The Development of Cutaneous Hypersensitiveness Following Intestinal Absorption of Antigenic Protein, ibid. **23**:176, 1925.

3. Anderson, A. F., and Schloss, O. M.: Allergy to Cow's Milk in Infants with Nutritional Disorders, Am. J. Dis. Child. **26**:451 (Nov.) 1923.

of hypersensitiveness develop. Eczematous infants are particularly favorable subjects for investigation of this problem because they may be studied at an age when new foods are introduced into their diets. The incidence of clinical and cutaneous hypersensitiveness to foods is known to be greater in eczematous than in noneczematous infants. Furthermore, in studying the complement fixation reactions for antibodies to egg white and cow's milk in the blood of these infants, György, Moro and Witebsky [4] demonstrated prozones.

The purpose of this report is to present observations on the immunologic reactions which follow ingestion of protein foods by normal and by eczematous infants and to consider these data in relation to the development of hypersensitiveness.

## METHODS

Specimens of blood were obtained for complement fixation and passive transfer tests without reference to the time of the previous meal, and intracutaneous tests were performed after collection. Complement fixation tests were done within two days of the time that specimens were obtained.

*Complement Fixation Tests.*—1. Test: Human serum was inactivated by heating at 56 C. for thirty minutes. It was then diluted in the proportion of 1:2.5 with physiologic solution of sodium chloride, and 0.1 cc. of the dilution was placed in each of two sets of 13 tubes. To these, 0.1 cc. each of 13 dilutions of antigen in multiples of 3 ranging from 1:100 to 1:53,144,100 and 2 units of complement diluted to 0.1 cc. were added. After mixture, one set of 13 tubes was placed in a water bath at 37 C. for one hour and the other in the ice box overnight. After fixation of the complement in a water bath or in the ice box, 0.1 cc. of hemolysin dilution (containing 2 units of sheep cell hemolysin) and 0.1 cc. of a 5 per cent suspension of sheep cells were added to each tube. (The tubes stored in the ice box were heated for ten minutes at 37 C. before the addition of hemolysin and cells.) Reactions were read after the mixtures were shaken and incubated at 37 C. for thirty and sixty minutes, respectively.

In some tests more extensive fixation of the complement was observed in the tubes stored overnight in the ice box. In order that confusion might be avoided, the results recorded in the text were obtained by that method.

2. Readings: The readings are recorded as follows: A 4 plus reaction indicates no hemolysis (complete fixation of the complement); a 3 plus reaction, slight hemolysis; a 2 plus reaction, hemolysis of about half the cells; a 1 plus reaction, almost complete hemolysis, and a 0 reaction, complete hemolysis (no fixation of complement).

3. Controls: These, which were run simultaneously with each test, are indicated in table 1.

4. György, P.; Moro, E., and Witebsky, E.: Eiklarempfindlichkeit bei Eczema infantum, Klin. Wchnschr. **9**:1012, 1930; Weitere Beobachtungen über trophallergische Hautempfindlichkeit im frühen Kindesalter, ibid. **9**:1435, 1930; Milchantikörper im Serum von Säuglingen, ibid. **10**:821, 1931; Weitere Erfahrungen über Trophallergie beim Eczema infantum, ibid. **11**:1172, 1932.

4. Preparation of Antigen Dilutions: The antigen designated as "cow's milk" was prepared from powdered skimmed milk, which was diluted to its original volume with water. Subsequent dilutions in multiples of 3 ranging from 1:100 to 1:53,144,100 were made with a physiologic solution of sodium chloride. Egg white was obtained from fresh hen's eggs and was diluted with a physiologic solution of sodium chloride.

5. Reagents: (*a*) Amboceptor. The sheep cell hemolysin was obtained from a commercial laboratory and was titrated frequently.

(*b*) Complement. The complement was obtained from the pooled serum of 3 guinea pigs and was collected on the day prior to each test. It was titrated against the standard hemolysin and was diluted so that 0.1 cc. contained 2 units.

(*c*) Indicator. Sheep blood cells taken less than five days previously were used. Shortly before the test, a sufficient quantity was washed four times in saline solution and made up to the equivalent of a 5 per cent suspension of sheep blood cells.

TABLE 1.—*Preparations for Control Tubes in Complement Fixation Tests**

| Control | Human Serum | Antigen Dilutions | Dilution of Complement (2 Units) | Psysiologis Solution of Sodium Chloride | Hemolysin Dilution (2 Units) | Red Blood Cells from Sheep, 5% | Satisfactory Result |
|---|---|---|---|---|---|---|---|
| Human serum (1:2.5 dilution) | 0.1 | ... | 0.1 | 0.1 | 0.1 | 0.1 | Complete hemolysis |
| Human serum (no dilution).. | 0.1 | ... | 0.1 | 0.1 | 0.1 | 0.1 | Complete hemolysis |
| Antigen..... | ... | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | Complete hemolysis |
| Hemolytic system..... | ... | ... | 0.1 | 0.2 | 0.1 | 0.1 | Complete hemolysis |
| Known positive serum..... | 0.1 | 0.1 | 0.1 | ... | 0.1 | 0.1 | No hemolysis |
| Sheep blood cells..... | ... | ... | ... | 0.4 | ... | 0.1 | No hemolysis |

* Duplicate sets of controls corresponded to the other portion of the test. In both sets, the constituents indicated in the first four columns were combined. One set was heated at 37 C. for one hour, and the other was kept in the ice box overnight. The constituents indicated in the last two columns were then added, and the preparations were incubated at 37 C. for one hour.

*Tests for Passive Transfer Antibody.*—One-tenth cubic centimeter of the patient's serum and 0.1 cc. of a known positive serum, as control, were injected intracutaneously in a normal person. Twenty-four to forty-eight hours later, approximately 0.02 cc. of a dilution of antigen was injected in each cutaneous site and in an unprepared area as a control. Positive reactions, indicated by a wheal and surrounding erythema, were read in fifteen minutes.

*Tests of Cutaneous Hypersensitiveness.*—Intracutaneous tests were performed by injecting approximately 0.02 cc. of a dilution of antigen into the skin of the external aspect of the upper arm. Tests for hypersensitiveness to cow's milk were done with a 1:100 dilution of powdered skimmed cow's milk and to egg white with a 1:1,000 dilution of fresh egg white. Reactions were read in fifteen minutes. In young infants, a positive reaction was often indicated by a localized area of edema and erythema without a well defined wheal and pseudopod-like extensions.

## SUBJECTS

Patients included in this study were admitted to the wards or the outpatient department of the New York Hospital. The majority lived at home and were

examined periodically, on visits to the clinic. In general, they remained in good health and received diets which are considered adequate by present standards. All were under 18 months old. They were divided into two groups: (1) normal infants, who remained free from cutaneous eruptions, and (2) infants suffering from infantile eczema. Infants with borderline involvement and infants who had transient eruptions which persisted for less than one month were excluded.

It should be emphasized that the term "infantile eczema" is applied throughout this communication in a specially defined sense. The cutaneous eruption usually develops during the first six months of life. Initial lesions appear as small papules or poorly defined erythematous areas which coalesce and may subsequently become moist. The serous secretion dries to form crusts. Pruritus is generally noted, and the lesions bleed easily when scratched. The eruption may be complicated by secondary infection during the acute stages. In a later stage the skin becomes thickened. Although facial lesions, especially of the cheeks, are usually the first to be observed and are often the most severe, the eruption may spread to the scalp, trunk and extremities. The antecrural and popliteal spaces are often involved. The condition is subject to exacerbations and remissions, the latter frequently occurring during the course of acute infections. Spontaneous recovery often occurs during the second year, but the disease may pass into the chronic form, which predominantly affects the flexures of the extremities and is frequently associated with asthma.

Infantile eczema, as previously described, is often confused with seborrheic dermatitis of the scalp, which may extend over the forehead ("cradle cap"), and eruptions of the diaper region due to chronic irritation, miliaria and impetigo. As all of these disorders are sometimes classified in the same group, it is difficult to compare the statistical reports of various authors. The European literature is particularly confusing in this respect.

## RESULTS

As already stated, the recorded data were derived from a study of intracutaneous, passive transfer and complement fixation tests for both egg white and cow's milk performed on a group of normal and of eczematous infants. Normal older children were included as controls. The results were considered with relation to ingestion of the proteins rather than age, as previous studies have shown that during infancy the immune response is the same regardless of the age at which the food is introduced.

Some infants were studied with repeated tests over periods of several months. When tests were done on the same infant both before and after introduction of a new food in the diet, the results were recorded under both categories. When there were repeated examinations on the same infant without change in diet, however, the results were recorded only once. The data in the tables which follow, therefore, represent the number of different infants studied in each group and not the total number of tests.

*Response of Normal Infants to Ingestion of Egg White.*—Tests were performed on 75 normal infants to determine the immunologic response to ingestion of egg white as a basis for comparison with a group of eczematous infants of similar age.

The first group studied consisted of 40 healthy infants who were reported never to have been fed egg in any form. The results of these tests, shown in table 2, demonstrate the absence of immunologic reactions to egg white in infants not fed egg, regardless of age or duration of breast feeding.

A second group comprised 20 infants who received boiled egg. In most instances this was fed in gradually increasing amounts, so that they received a whole egg daily after about one month. With the exception of a positive complement fixation reaction in 1 infant, who had received a whole soft-boiled egg daily during the previous six weeks, the results were negative. It is possible that other positive reactions might have been found if these infants had been tested repeatedly a few weeks after egg was introduced into their diets.

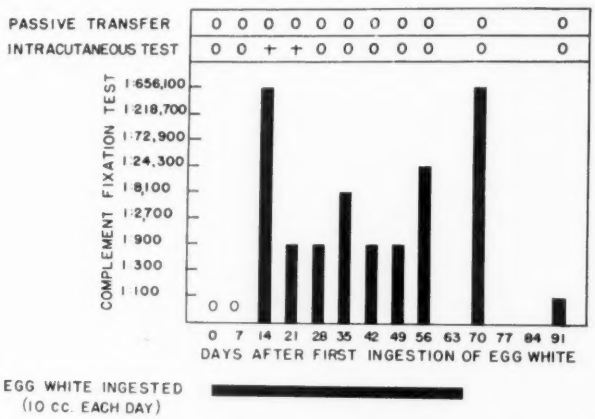


Chart 1.—The immunologic response of a normal infant to initial ingestion of raw egg white. At the age of 3 months 10 cc. of egg white was fed each day for sixty-eight days.

When normal infants were fed raw egg white in adequate amounts, however, sufficient protein was absorbed in antigenic form to stimulate the production of antibodies demonstrable by complement fixation and by transient cutaneous hypersensitiveness. Passive transfer antibodies were not detected. Nine infants were fed 5 to 10 cc. of raw egg white daily for thirty-one to sixty-eight days, and tests were repeated at intervals of about seven days. In 5 of 9 patients transient cutaneous hypersensitiveness developed between the ninth and the fourteenth day. A serologic response to absorption of antigen was demonstrated by the development of complement fixation antibodies in from nine to forty days. The reactions noted in 1 normal infant are presented graphically in chart 1.

These observations confirm the previous reports of other authors, who demonstrated precipitins, complement fixation or transient cutaneous hypersensitiveness in normal infants when large amounts of crystalline egg albumin were fed [2b] or when egg white was injected subcutaneously.[5] It must be emphasized, however, that such reactions are observed only when egg is introduced in unusual amounts and that they do not follow ingestion of cooked egg in the amounts usually fed to infants.

*Response of Eczematous Infants to Ingestion of Egg White.*—In order to compare the immunologic reactions of eczematous infants with those of the normal infants previously described, groups of the former were studied in a similar manner. The results are summarized in table 2.

TABLE 2.—*Results of Intracutaneous and Serologic Tests for Antibodies Against Egg White in Normal and in Eczematous Infants*

| Group | Number of Subjects | Intracutaneous Tests | | Passive Transfer Tests | | Complement Fixation Tests | | | Age, Months | | Interval Between First Egg Feeding and Day of Test, Months | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | + | — | + | — | + (Prozone) | + (No Prozone) | — | Range | Average | Range | Average |
| Normal infants never fed egg | 40 | 0 | 40 | 0 | 40 | 0 | 0 | 40 | 1-15 | 4.7 | ..... | ... |
| Normal infants fed cooked egg | 20 | 0 | 20 | 0 | 20 | 0 | 1 | 19 | 5-18 | 11.0 | 1.0-12.0 | 3.0 |
| Normal infants fed 5 to 10 cc. of raw egg white daily | 9 | 5 | 4 | 0 | 9 | 0 | 5 | 3 | 1-11 | 4.6 | * | ... |
| Eczematous infants never fed egg | 21 | 10 | 11 | 7 | 14 | 5 | 0 | 16 | 1- 9 | 4.5 | ..... | ... |
| Eczematous infants fed cooked egg | 16 | 15 | 1 | 6 | 10 | 9 | 0 | 7 | 3-14 | 9.0 | 0.5-7.0 | 4.4 |

* All infants were tested repeatedly at intervals of about seven days.

Almost all eczematous infants who had been fed egg at some time in the past showed evidence of an immunologic response. Of 16 studied, 15 had cutaneous hypersensitiveness to egg white; the blood of 6 contained passive transfer antibodies, and 9 had positive complement fixation reactions with prozones. In the majority, only cooked egg in extremely small quantities had been fed several weeks or months before the test and had subsequently been discontinued because of vomiting or increase in intensity of the cutaneous eruption or on suspicion. This group may be compared with the normal infants, who received cooked egg regularly and in larger quantities and rarely showed any reaction.

Among the eczematous infants, who were followed with repeated determinations, several patterns of reaction were observed. In some,

5. Moro, E.: Eczema infantum und Dermatitis seborrhoides, Berlin, Julius Springer, 1932, p. 87. Woringer, P.: Deux sortes d'anticorps ovalbuminiques dans le sang des nourissons, Compt. rend. Soc. de biol. **109**:206, 1932.

the response was characterized by complement fixation reactions and by cutaneous hypersensitiveness which lasted for only a few months (chart 2*A*). In others, the response was more pronounced and was characterized by persistent cutaneous hypersensitiveness and by passive transfer and complement fixation antibodies (chart 2*B*).

Some eczematous infants who had never ingested egg were also found to have positive immune reactions. Of 21 infants observed, 10 were found to be hypersensitive by intracutaneous test; the blood serums of 7 contained passive transfer antibodies, and 5 showed com-

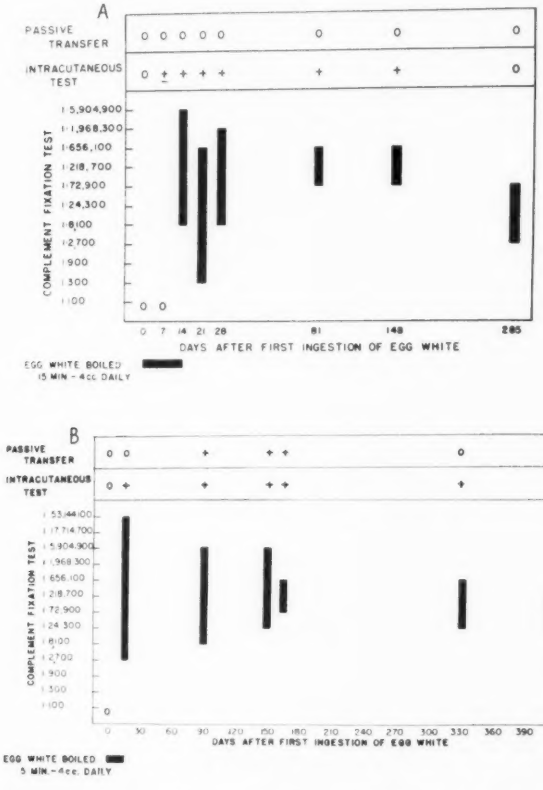


Chart 2.—The immunologic response of eczematous infants to initial ingestion of heated egg white. *A*, from the age of 3 months, a child was fed 4 cc. of egg white, boiled fifteen minutes, each day for fourteen days. Mild eczema of the face, neck and shoulders appeared at the age of 6 weeks and persisted for seven months. At the age of 10 months, small amounts of egg were given again without recurrence of the eruption. *B*, from the age of 3½ months, a child was fed 4 cc. of egg white, boiled five minutes, each day for fourteen days. Egg was not fed again during the period of observation. Severe eczema appeared on the face at the age of 3 weeks and rapidly spread over the rest of the body. Although the eruption gradually diminished in severity, it was still present at the age of 19 months.

plement fixation reactions. Prozones (negative reactions in tubes containing low dilutions of antigen and positive reactions in tubes containing high dilutions) were noted in the 5 positive complement fixation reactions. Tests on several of these infants were repeated at intervals, and it was observed that the pattern of response closely resembled that which followed ingestion of egg white by other eczematous infants. The results of tests on 1 of these infants are shown in chart 3.

The presence of antibodies in this group is difficult to explain. There is no evidence that the histories of absence of ingestion of egg were incorrect, as the mothers were questioned carefully and as, furthermore, the majority of these infants were in the age group in which egg is not usually fed. The mothers denied having eaten eggs in extraordinary quantities during pregnancy.

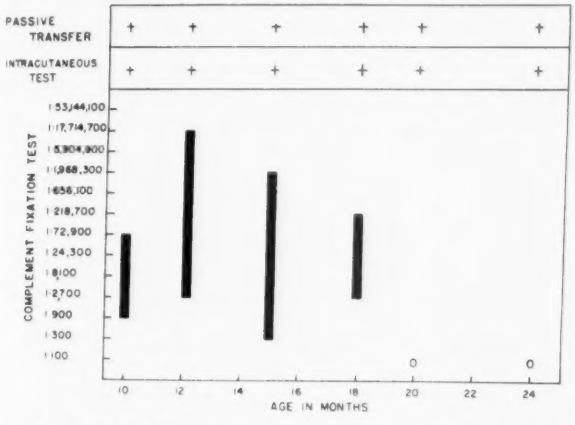


Chart 3.—Reactions observed in an eczematous infant reported never to have been fed egg. Eczema appeared at the age of 1 month, remained severe during the first year and gradually subsided, but was still present after two years.

Seven mothers of egg-sensitive infants from the previous group were studied in relation to passive sensitization by placental transmission of antibodies. One gave a history of hypersensitiveness to egg and had a positive cutaneous reaction and passive transfer antibody; another had only a positive cutaneous reaction. It is possible that hypersensitiveness may have been transmitted in the 2 cases. Tests on the other mothers gave negative results. Passive sensitization by placental transmission of antibodies has been conclusively demonstrated in experimental animals.[6] There is little evidence, however, that it is an important

6. Ratner, B.; Jackson, H. C., and Greuhl, H. L.: Transmission of Protein Hypersensitiveness from Mother to Offspring: IV. Passive Sensitization in Utero, J. Immunol. **14**:291, 1927. Cohen, M. B., and Woodruff, B. H.: Observations on the Transmission of Passive Anaphylactic Sensitivity in the Guinea Pig, J. Allergy **8**:437, 1937.

mechanism in sensitization of infants, although there are isolated reports of sensitivity to the same protein in mother and child.[7] Attempts to demonstrate placental transmission of passive transfer antibodies by examination of blood from the umbilical cords of infants have been unsuccessful.[8]

Secretion of egg white in the breast milk was also considered. One mother gave a history of taking several raw eggs with sherry daily during lactation. All infants in this group were nursed, and it is possible that transmission of egg white through the breast milk may have provided adequate stimulation. This point will be discussed in more detail later.

*Response of Normal Infants to Ingestion of Cow's Milk.*—Negative reactions to intracutaneous, passive transfer and complement fixation

TABLE 3.—*Results of Intracutaneous and Serologic Tests for Antibodies Against Cow's Milk in Normal and in Eczematous Infants*

| Group | Number of Subjects | Intracutaneous Tests | | Passive Transfer Tests | | Complement Fixation Tests | | | Age, Months | | Interval Between First Cow's Milk Feeding and Day of Test, Months | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | + | — | + | — | + (Prozone) | + (No Prozone) | — | Range | Average | Range | Average |
| Normal infants never fed cow's milk | 24 | 0 | 24 | 0 | 24 | 0 | 0 | 24 | 0- 7.0 | 2.3 | ..... | ... |
| Normal infants fed cow's milk | 46 | 0 | 46 | 0 | 46 | 7 | 23 | 16 | 1.0-15.0 | 6.0 | 0.5-12.0 | 4.6 |
| Eczematous infants never fed cow's milk | 5 | 0 | 5 | 0 | 5 | 0 | 0 | 5 | 1.5- 6.0 | 3.8 | ..... | ... |
| Eczematous infants fed cow's milk | 28 | 10 | 18 | 1 | 27 | 21 | 1 | 6 | 2.0-18.0 | 7.1 | 0.5-16.0 | 4.9 |

tests for antibodies to cow's milk were observed in all normal infants who had never received cow's milk. This group comprised 24 breast-fed infants ranging in age from birth to 7 months. The results of tests for immune reactions to cow's milk in this and in other groups are summarized in table 3.

Positive reactions to complement fixation tests for antibodies to cow's milk were recorded for 30 of 46 normal infants who had received cow's milk. This observation is in agreement with results of a previous investigation, in which a large group of infants was considered in rela-

7. Ratner, B.: Possible Causal Factor of Food Allergy in Certain Infants, Am. J. Dis. Child. **36**:277 (Aug.) 1928. Ratner, B., and Greenburgh, J. E.: Congenital Protein Hypersensitiveness Transmitted from Allergic Mother to Child, J. Allergy **3**:149, 1932.

8. Bell, S. D., and Eriksson, Z.: Studies in the Transmission of Sensitization from Mother to Child in Human Beings: I. Transfer of Skin Sensitizing Antibodies, J. Immunol. **20**:447, 1931.

tion to duration of feeding of cow's milk.[1] Results of intracutaneous and of passive transfer tests were regularly negative. Had the former been done approximately two weeks after the initial ingestion of cow's milk, positive reactions probably would have been observed in some cases. The serologic response to ingestion of cow's milk by a normal infant is shown in chart 4.

*Response of Eczematous Infants to Ingestion of Cow's Milk.*—Eczematous infants who were entirely breast fed prior to examination had negative reactions for antibodies to cow's milk. Only 5 infants, aged from 6 weeks to 5 months, were included in this group.[9] The results obtained were identical with those for a larger group of normal breast-fed infants.

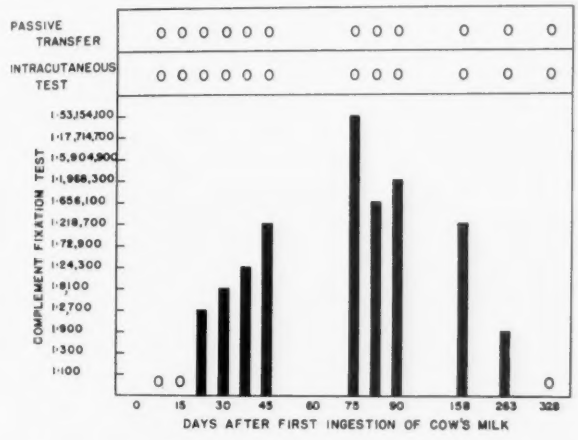


Chart 4.—The immunologic response of a normal infant to the initial ingestion of cow's milk. The infant was weaned, and feeding of cow's milk was started on the seventh day.

In contrast to the eczematous breast-fed infants, positive reactions were frequently observed among those who received cow's milk. Of 28 infants examined, 10 had positive intracutaneous reactions; 1 a positive passive transfer reaction, and 22, positive complement fixation reactions for antibodies to cow's milk. For 21 of the latter there were negative reactions in the tubes which contained strong concentrations of antigen and positive reactions with greater dilutions (prozone) on 1 or more occasions. The 6 infants who had negative complement fixation reactions had received cow's milk for less than one or more than eight months.

9. Eczema is seldom observed prior to the second or third month of life, at which age most infants have received cow's milk.

The response to ingestion of cow's milk by eczematous infants was characterized by various degrees of deviation from the normal pattern. In some, positive reactions were observed for only a few months (chart 5 *A*), while in others they were noted over longer intervals (chart 5 *B*).

*Control Tests on Normal Older Children.*—In order to control the technics employed, intracutaneous, passive transfer and complement

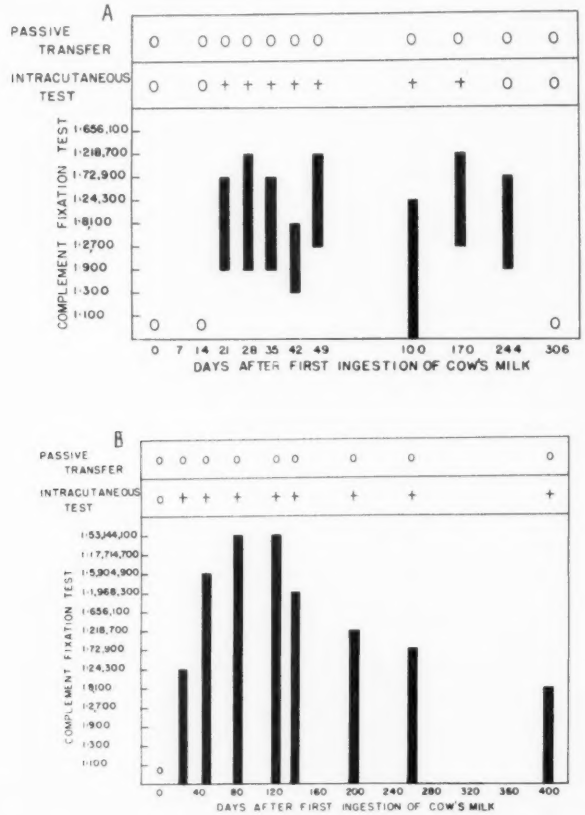


Chart 5.—The immunologic response of eczematous infants to the initial ingestion of cow's milk. *A*, the infant received breast milk for two and one-half months and was weaned abruptly. Eczema was first observed at the age of 2 months and persisted through the eighth month. *B*, the infant received breast milk for two months, both breast and cow's milk through the eighth month and only cow's milk thereafter. Eczema was first observed shortly after cow's milk was introduced into the diet. It never became severe but was present intermittently during the following seven months.

fixation tests for cow's milk and for egg white were done on a group of 16 normal children between 3 and 13 years old. The results were negative.

*The Prozone Phenomenon in Complement Fixation Tests.*—Prozones are frequently demonstrable when complement fixation tests are done with the blood of eczematous infants. When constant amounts of serum are set up against progressive dilutions of antigen, negative reactions are observed in the tubes containing low dilutions of antigen and positive reactions in those containing higher dilutions, up to a point at which negative reactions again appear. This was observed by Györgi, Moro and Witebsky [4] and subsequently by Strobl and Wasitzky,[10] Woringer [11] and Zambrano and Pezza.[12]

The tests done during the present study support the hypothesis that this phenomenon is usually demonstrable with the blood of eczematous and seldom with the blood of normal infants. Thirty-eight positive complement fixation reactions were obtained with the blood of eczematous infants when the antigen was egg white.[13] Of that number, 37 were positive in the tubes containing the higher dilutions of antigen and negative in those containing the lower dilutions. The remaining test gave a positive reaction in all tubes. When cow's milk was used as antigen, 70 positive reactions were obtained with the blood of eczematous infants, and prozones were demonstrable in 40 reactions (57 per cent). The range of positive reactions varied in different patients and on repeated determinations for the same patient at weekly or monthly intervals. Protocols of typical tests illustrating the usual range and the prozone phenomenon are recorded in table 4.

When low and high dilutions of antigen were tested against progressive dilutions of serum, positive complement fixation reactions were obtained only with the greater concentrations of serum. Dilution of serum did not alter the level of antigen dilution at which positive reactions were detected in specimens which demonstrated prozones. Furthermore, this experiment showed that serums with which prozones were obtained were not necessarily stronger (did not react with greater dilutions of serum) than those which showed positive reactions in the usual range. Protocols of such titrations are recorded in table 5.

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10. Strobl, A., and Wasitzky, A.: Untersuchungen über die alimentäre Allergie des Ekzemkindes, Monatschr. f. Kinderh. **54**:53, 1932.

11. Woringer, P.: Recherches sur la réaction de fixation du complément dans la holo-allergie ovalbuminique, Compt. rend. Soc. de biol. **111**:726, 1932.

12. Zambrano, E., and Pezza, E.: Ricerche sull'allergia da latte di vacca e da albume d'uovo nei bambini con manifestazioni cutanee della diatesi essudativa, Pediatria **43**:642, 1935.

13. These figures do not check with those in the previous tables, as they include positive reactions with the blood of the infants who were tested more than once.

The problem of the prozone phenomenon in complement fixation reactions has been studied extensively by Sharma [14] and Hahn.[15] Although prozones could be demonstrated by manipulation of components of the antigen-antibody system when the blood of artificially immunized normal infants or rabbits was used, they were seldom observed with the standard technic. The frequent occurrence of prozones in tests done with the blood of eczematous infants has not been adequately explained.

TABLE 4.—*Protocols of Complement Fixation Tests on Serum from a Normal* and from an Eczematous† Infant*

| Antigen Dilutions (Serum Dilution Constant) | Serum A (Usual Range of Positive Reactions) | | Serum B (Prozone) | |
|---|---|---|---|---|
| | Milk | Egg | Milk | Egg |
| 1:100 | ++++ | ++++ | 0 | 0 |
| 1:300 | ++++ | +++ | 0 | 0 |
| 1:900 | ++++ | +++ | ++++ | 0 |
| 1:2,700 | ++++ | +++ | ++++ | 0 |
| 1:8,100 | ++++ | ++ | ++++ | ++ |
| 1:24,300 | ++++ | ++ | ++++ | +++ |
| 1:72,900 | +++ | 0 | ++++ | ++++ |
| 1:218,700 | 0 | 0 | +++ | ++++ |
| 1:656,100 | 0 | 0 | ++ | ++++ |
| 1:1,968,300 | 0 | 0 | 0 | ++++ |
| 1:5,904,900 | 0 | 0 | 0 | ++ |
| 1:17,714,700 | 0 | 0 | 0 | 0 |
| 1:53,144,100 | 0 | 0 | 0 | 0 |

* Serum A.
† Serum B.

TABLE 5.—*Protocols of Complement Fixation Tests in Which Low and High Dilutions of Antigen Were Tested Against Progressive Dilutions of Serum*

| | Serum A (Usual Range of Positive Reactions) | | | | Serum B (Prozone) | | | |
|---|---|---|---|---|---|---|---|---|
| | Milk | | Egg | | Milk | | Egg | |
| Antigen dilution | 1:100 | 1:24,300 | 1:100 | 1:24,300 | 1:100 | 1:24,300 | 1:100 | 1:24,300 |
| Serum dilution | | | | | | | | |
| 1:2.5 | ++++ | ++++ | ++++ | ++ | 0 | ++++ | 0 | +++ |
| 1:5 | +++ | ++++ | ++++ | + | 0 | ++++ | 0 | + |
| 1:10 | + | + | ++++ | 0 | 0 | +++ | 0 | 0 |
| 1:20 | 0 | 0 | +++ | 0 | 0 | + | 0 | 0 |
| 1:40 | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 |
| 1:80 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1:160 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1:320 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

*Relation of the Prozone Phenomenon to the Passive Transfer Reaction.*—Although the prozone phenomenon in complement fixation reactions seems to be closely associated with hypersensitiveness, it cannot be used as a laboratory test for passive transfer antibody. An analysis of

14. Sharma, B. M.: Beiträge zur serologischen Analyse des Eiklars, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:79, 1932.

15. Hahn, F.: Ueber Doppelzonen bei der Reaktionsfähigkeit von Eiklar mit Eiklarantiserum, Ztschr. f. Immunitätsforsch. u. exper. Therap. **87**:95, 1936.

the results of tests performed on 32 samples of blood serum from eczematous infants which contained passive transfer antibody for egg white revealed the fact that only 18 were positive by complement fixation. All of these reactions were positive only with the higher dilutions of antigen. Conversely, 20 samples of blood serum from eczematous infants which did not contain the factor necessary for transfer of hypersensitiveness to egg white demonstrated prozones in complement fixation tests. When cow's milk was used as antigen, prozones were observed frequently in tests made with blood obtained from eczematous and occasionally with that from normal infants, although passive transfer of hypersensitiveness to milk was not demonstrable.

It is interesting to note, however, that the only positive complement fixation reaction for antibody to milk or egg white in a person over 5 years of age ever observed in this laboratory was in the blood serum of an 11 year old boy which contained passive transfer antibody for egg white. This showed the characteristic prozone.

## COMMENT

The following discussion is confined to a brief consideration of the information obtained during the course of this investigation, which is concerned with the development of hypersensitiveness in infancy. One school of thought supports the view that the tendency to develop hypersensitiveness is specifically inherited and is not dependent on either contact with antigen or transmission of antibodies from the mother. This hypothesis is based principally on the observation that infants may show cutaneous reactions to certain foods, particularly egg white, prior to ingestion and discounts the possibility that such foods may be transmitted by breast milk or placental circulation. Smyth and Bain [16] and others have observed the appearance of positive cutaneous reactions for foods in young infants when they were not ingesting the foods to which they became sensitive.

Another hypothesis is that, as in experimental animals, hypersensitiveness in human beings may develop actively in response to stimulation of the tissues by contact with antigen or passively by placental transmission of antibodies. Passive transmission of antibodies has been discussed previously; it was concluded that, although it is demonstrable in experimental animals, there is little evidence that it plays an important role in the sensitization of infants. Evidence of active sensitization is somewhat more convincing but not conclusive.

It seems probable that if a sufficient amount of antigen enters the circulation in the majority of normal persons there may be an immune

16. Smyth, F. S., and Bain, K.: The Direct Skin Test in Allergy, J. Allergy **2**:316, 1931.

response. In normal infants, not subject to allergic disorders, positive cutaneous reactions and antibodies demonstrable by precipitin and complement fixation tests develop after the initial ingestion of adequate amounts of protein foods. Somewhat more striking is the response observed in infants who probably absorb larger amounts of antigen from the intestinal tract during the acute phase of intestinal disorders and in persons who have serum sickness after therapeutic injection of horse serum. In these exaggerated types of response, passive transfer antibodies may also be demonstrated in the circulating blood at the peak of the reaction. It must be emphasized, however, that in these conditions serologic and cutaneous reactions are often temporary.

Although the immunologic response of eczematous infants to ingestion of protein foods follows the same general pattern as that of normal infants, certain deviations are frequently observed. The results of this investigation suggest that positive reactions may be detected after ingestion of much smaller quantities of egg white. Furthermore, strongly positive and more persistent cutaneous and passive transfer reactions are often noted, and prozones are more frequently demonstrable by complement fixation.

This difference in response may be qualitative or quantitative. The possibility that a qualitative difference in the antibody is demonstrable by the prozone phenomenon in complement fixation reactions has been discussed. Since prozones are occasionally observed in tests done with blood serums of noneczematous infants, this is of questionable value as a differential point. Furthermore, the presence of passive transfer antibody is not a distinguishing feature of the so-called allergic person because it is found in the blood of normal infants suffering from nutritional disorders and in the blood of persons with serum sickness.

The results of this investigation support the belief that the difference is one of intensity rather than character. Immunologically, eczematous infants cannot be sharply differentiated from the noneczematous because within each group the response varies in degree. The tendency to respond to a minimal stimulus seems to vary from the absence of reaction noted in some normal infants to the exaggerated response observed in some of the eczematous group.

If the difference is quantitative, the degree of response may depend on increase either in stimulation or in the reactive capacity of the tissues. Increased intestinal permeability may lead to greater absorption and antigenic stimulation, but this cannot be proved because there are no available methods for quantitative estimation of small amounts of antigens in the circulation or in the tissues.

The capacity of tissues to produce antibodies after minimal stimulation may be increased in eczematous infants. This hypothesis is

supported by the observation that they may have an extensive immune response after ingestion of quantities of egg white which are not effective in normal infants and that serologic reactions may persist for long intervals without further stimulation.

Since immune responses are observed in eczematous infants after ingestion of small quantities of egg white, it is conceivable that even the minute amounts which may reach the infant by placental or lacteal transmission may also be adequate. Direct evidence of placental transmission of antigens in human beings is lacking, and proof that foreign proteins are secreted in breast milk is subject to controversy.[17]

In conclusion, the available data suggest that, at least in some infants, hypersensitiveness may develop after contact with ingested foods. Furthermore, it seems possible that an additional intrinsic or extrinsic factor, possibly hereditary, may produce in eczematous infants an exaggeration of the normal response and that this results in a more pronounced and more persistent immune reaction. The variability in intensity of response in both normal and eczematous infants seems to indicate, however, that the difference between the two groups may be quantitative rather than qualitative.

## SUMMARY

The immunologic response to absorption of antigenic substances in cow's milk and egg white by normal and by eczematous infants was studied by determination of complement fixation, passive transfer and intracutaneous reactions before and after the initial ingestion.

Intracutaneous, complement fixation and passive transfer tests for antibodies to cow's milk gave negative results for both normal and eczematous infants who received only human milk.

After ingestion of cow's milk, an immunologic response characterized by the development of specific antibodies demonstrable by complement fixation was observed in normal and in eczematous infants. In 35 per cent of the eczematous infants studied there also developed cutaneous hypersensitiveness to cow's milk. Passive transfer antibody for cow's milk was detected in only 1 eczematous infant.

Temporarily positive intracutaneous and complement fixation reactions developed after the initial ingestion of raw egg white by normal infants, but no reactions were noted for this group after ingestion of heated egg white.

17. Donnally, H. H.: The Question of the Elimination of Foreign Protein (Egg-White) in Woman's Milk, J. Immunol. **19**:15, 1930. György, P.: Eiklar-Antigen in der Frauenmilch, Jahrb. f. Kinderh. **132**:1, 1931. Stuart, H. C.: The Excretion of Foreign Protein in Human Milk, Am. J. Dis. Child. **25**:135 (Feb.) 1923. Smyth, F. S., and Bain, K.: Enteral Absorption of the Antigen Secretion in Human Milk, J. Allergy **2**:282, 1930.

Eczematous infants who were fed small amounts of heated egg white had specific cutaneous, complement fixation or passive transfer reactions. Furthermore, some eczematous infants who had never ingested egg were found to have similar reactions. It is possible that the latter may have absorbed egg white transmitted through breast milk or the placental circulation.

Prozones were demonstrated frequently in complement fixation tests made with the blood of eczematous infants and infrequently in those made with the blood of normal infants. The demonstration of a prozone was not found to be a satsfactory test for passive transfer antibody.

An immunologic response to intestinal absorption of protein is a physiologic and innocuous process in the majority of infants. In others, particularly those suffering from infantile eczema, it may be associated with the development of a persistent state of tissue hypersensitiveness.

Miss Frances G. Crawford gave technical assistance.

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# EXPERIMENTAL PARALYSIS IN MONKEYS COMPLETELY RECOVERED FROM POLIOMYELITIS

## PRODUCED BY CULTURES OF MATERIAL FROM PATIENTS WITH MEASLES

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DETROIT

It has been stated that there are few second attacks of poliomyelitis.[1] However, reports of such attacks can be found in the literature. It has been suggested that in many cases the paralyses have been due not to actual reinfection with the virus of poliomyelitis but to some other acute infectious disease which involved the few peripheral nerve fibers remaining after the previous severe attack of poliomyelitis.[1] As a result, the same objective findings would be noted with the second as with the first attack of paralysis. Macacus rhesus monkeys that contract poliomyelitis sometimes recover with massive atrophies. The object of the experiments described in this article was to determine if paralyses would again develop if these animals were subsequently inoculated with the causative factor of some acute infectious disease.

### MATERIAL AND METHODS

Thirteen animals, most of which had recovered from a severe attack of poliomyelitis, were used in this experiment. Their condition at the time of the experiment was as follows: Monkey 684 had survived several injections of poliomyelitis virus without having contracted the disease; monkey 690 had atrophy and fixation of the muscles of both legs, including the feet and thighs, the left hand, the left upper extremity, the right hand and the right upper extremity; monkey 882 had atrophy of the muscles of both feet, the left leg, the right thigh and the left hand; monkey 898 had atrophy and fixation of the muscles of the left leg; monkey 911 had atrophy and fixation of the muscles of the left lower

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1. Toomey, J. A.: The Question of Second Attacks of Poliomyelitis in the Human Being, Am. J. Dis. Child. **56**:969 (Nov.) 1938.

extremity, the right thigh, the right hand and the right arm; monkey 1149 had atrophy and fixation of the muscles of the right lower extremity, the right thigh, the left upper extremity and the right hand; monkey 1153 had atrophy of the muscles of both legs; monkey 1170 had atrophy and fixation of the muscles of the left lower extremity, the right thigh and the right hand; monkey 1176 had atrophy of both gastrocnemius muscles, the adductor and quadriceps muscles on the left and the muscles of the left upper extremity; monkey 1180 had atrophy of the muscles of the left thigh and left hand; monkey 1317 had atrophy of some of the muscles of the left leg, including the foot and the thigh; monkey 1321 had atrophy and fixation of the muscles of both legs, the right thigh and the left forearm; monkey 1356 had atrophy of the muscles of both legs.

Cultures of material obtained from the throats of patients ill with measles were planted on 20 per cent human hemoglobin agar and allowed to grow for twenty-four hours. The nutrient blood was obtained from patients in the acute stages of measles. Five cubic centimeters of a physiologic solution of sodium chloride were added to the culture, and an emulsion was made of the growth and poured into an atomizer. About 2 cc. of this suspension was blown into the nostrils of the monkeys, and 1 cc. was injected intratracheally after the trachea had been anesthetized. The procedure was repeated on the second day.

In all animals studied the spinal cords were sectioned at the lumbar, upper lumbar, midthoracic, upper thoracic and cervical areas. Sections were prepared with hematoxylin and eosin and with the Nissl, neuroglial and myelin stains.

## PROTOCOLS

Eight animals showed furring, and their activity was retarded for a few days, but they did not have any paralyses. Five had reactions, as will be noted.

Monkey 690.—On Dec. 8, 1937, this animal was given its first instillation and injection. The next day it showed furring, had lost the use of its voice and had floppy movements of the extremities. It had dyspnea, air hunger and possibly pneumonia. On December 10 the animal was lying down. The arms were weak and floppy. The monkey could not get up; its movements were incoordinated, and it breathed with difficulty. It was unable to cry. Death occurred on the same day.

An autopsy performed on the day of death showed that the lungs were not consolidated; they were pinkish and crepitant and floated in water. There was no fluid in the chest, and on section of the lungs no exudate was found. The liver, spleen and intestines were normal. The trachea was also normal, and there was no sign of congestion or inflammation near the point of injection. The spinal cord and the surfaces of the posterior cerebral lobes of the brain were hyperemic.

Microscopic Report: There were no signs of inflammation in sections of the spinal cord. All of the cells stood out distinctly.

Monkeys 882 and 898.—These animals were infected with cultures from R.F. and E.K., patients with measles, on November 15. The culture plate of E.K. contained large white staphylococci and colonies of small, fine streptococci. On the plate of R.F. there were large colonies of Staphylococcus aureus and fine black streptococci.

For the first two days after injection monkey 882 was listless and furred. On November 18 the hindlegs were weaker than usual. On November 19 the animal had dyspnea and air hunger; it was listless, and the hindlegs dragged. On November 20 there was slight improvement. On November 21, 22 and 23 the

monkey had generalized weakness. On November 25 it was extremely sick; the breathing was rasping, the animal was obviously paralyzed, and the tail dragged. The monkey was killed on the same day.

At autopsy all the organs seemed normal save the heart, which was enlarged. There was slight mucous exudate in the bronchi and the trachea. There was no inflammation in the trachea at the point of the injection. The lungs were normal. Cultures were made of blood from the heart and of the bronchial exudate; both were negative.

Microscopic Report: Sections of the spinal cord showed a decrease in the number of motor cells, but there was no evidence of any acute inflammatory changes.

MONKEY 898.—The day after instillation and injection this animal showed furring and was listless. On November 17 it had difficulty in respiration, with flaring of the nostrils, dyspnea and air hunger. On November 18 there were obvious weaknesses of muscle groups, especially of the hindquarters. On November 19 the animal had complete paralysis of both lower extremities, dyspnea and tachypnea. On November 20 there was some improvement in breathing, but the hand had now become weak. On November 21 the animal was dragging the hindquarters; it was listless, and there was a nasal discharge. The monkey died at noon that day.

At autopsy there was a small area of consolidation (about 4 by 5 mm.) in each lung. The lungs, however, floated when immersed in water. A frothy exudate was obtained when they were compressed, and the bronchi were filled with this exudate. The other organs appeared to be normal, although there was obvious enlargement of the mesenteric lymph nodes. The trachea was normal at the point of injection. The spinal cord was hyperemic. Cultures of blood from the heart yielded hemolytic streptococci and staphylococci. Pure hemolytic streptococci were obtained in a culture of the exudate obtained from the bronchi and the consolidated areas of the lungs.

Microscopic Report: Sections of the spinal cord showed a definite absence of motor cells in many areas, due to the old disease, but no sign of any inflammatory reactions.

MONKEY 911.—On December 8 the virus was instilled and injected as described. On December 9 the monkey had dyspnea and air hunger and was beginning to have weaknesses of the muscles. On December 10 it was getting better. On December 25 it was well. On Jan. 25, 1938, the material obtained from patients R.B. and L.P. was inoculated intratracheally and instilled intranasally. On January 26 the animal had anorexia but otherwise was well. By January 28 it had recovered.

MONKEY 1149.—On Dec. 1, 1937, this animal received an injection and instillation of the material obtained from C.N.L. and P.H., patients with measles. On December 3 the monkey showed no change. On December 4 it received another injection and nasal instillation of the material. On December 5 the extremities were weak, and the legs were nearly floppy. The monkey was killed on December 6.

At autopsy the area at the site of the tracheal injection was inflamed. There was slight consolidation in the lower lobe of the right lung; the lungs were cherry red, were frothy when compressed and floated in water. The trachea and the bronchi were filled with mucus. The retroperitoneal lymph nodes were swollen. There was hyperemia of both posterior cerebral lobes and of the spinal cord. Hemolytic streptococci were isolated from the blood of the heart.

Microscopic Report: Here, as in the other instances, there was no evidence to explain why paralysis should have occurred. There was probably a decrease in the number of motor cells and in neuroglial elements, but there was no acute inflammatory reaction.

REPORT ON PERIPHERAL NERVES

Since microscopic examination of the spinal cords of these 5 animals showed nothing that would indicate an acute infection which would cause paralysis, a few sections of the peripheral nerves were studied by polarized light. Sections taken from the sciatic, femoral, brachial plexus and vagus nerves of animals 1149 and 690 were placed in a 10 per cent solution of formaldehyde. These were studied between Nicol's prisms according to the method described by Sutton, Setterfield and Krauss[2] and referred to by us.[3]

MONKEY 1149.—The specimen of the vagus nerve was characterized by slight fibrosis. No positive statement could be made, but it seemed possible that this condition represented the replacement fibrosis as a sequela of diffuse wallerian degeneration at some preceding date. The nerve tissue appeared perfectly normal.

In the sciatic nerve could be seen slight fibrosis, probably of the replacement variety.

In the femoral nerve some of the larger nerve fibers appeared to be swollen, being particularly characterized by an edematous, isotropic neurokeratin network. The remaining nerve fibers appeared normal. The nerve trunk showed a large amount of fibrosis, probably of the replacement type.

In the brachial plexus there was mild fibrosis. In one trunk the nerve fibers were characterized by an unusually great number of Schmidt-Lantermann incisures. These structures were large, regular in outline, isotropic and so numerous and divergent from the true axis-cylinders that the latter structures were uncovered throughout most of their length. No significance could be attached to this observation. Otherwise the nerves appeared normal.

MONKEY 690.—The brachial plexus was normal.

In the femoral nerve one nerve trunk showed slight fibrosis, probably a replacement variety. Another trunk, otherwise normal, showed numerous nerve fibers which were swollen and had some peripheral irregularity of the non-neurofibrillated portion of the axis-cylinders.

In the sciatic nerve one nerve trunk was normal; the other was characterized by replacement fibrosis. In this nerve one fasciculus was encountered in which the nerve fibers showed extreme vacuolation and swelling of the non-neurofibrillated portion of the axis-cylinders and of the Schmidt-Lantermann incisures. Otherwise the nerve appeared normal.

Wallerian Degeneration: In almost every case the nerves from the monkeys showed evidence of wallerian degeneration at some preceding date. This statement is based on the presence of numerous cordlike strains of connective tissue which were interpreted as evidence of metaplasia of the neurilemma sheath following degeneration of the nerve fiber. These connective tissue cords were of small diameter and in most cases were scattered diffusely throughout the trunk. Four of the nerve trunks showed only evidence of acute degeneration, and in these cases it was extremely slight. There is no explanation for the paralysis described.

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2. Sutton, T. S.; Setterfield, H. E., and Krauss, W. E.: Nerve Degeneration Associated with Avitaminosis A in the White Rat, Bulletin 545, Ohio State University, College of Agriculture, Agricultural Experiment Station, 1934.

3. Toomey, J. A., and Weaver, H. M.: Poliomyelitis Virus and the Degeneration of Peripheral Nerves, Am. J. Dis. Child. **53**:79 (Jan., pt. 1) 1937.

## COMMENT

Thus far it is not possible to state definitely why these monkeys had paralyses after the use of the material from patients with measles. The condition was not merely the weakness that resulted from generalized infection, since in control animals a like condition never developed. These animals had obvious paralyses and showed the objective changes seen after an attack of poliomyelitis. Although unproved, our opinion is that the exact reason for the paralysis probably lies in the condition of the peripheral nerves. Too few of the latter were studied to rule out the peripheral nerves entirely. Although the reason why paralyses occurred in these animals is not certain, it is obvious that they were not associated with any morphologic changes in the spinal cord. Thus there must be some condition other than an involvement of the motor cells of the central nervous system to explain the production of these paralyses. It can be concluded that such paralyses cannot be attributed to second attacks of poliomyelitis.

## SUMMARY AND CONCLUSION

Some Macacus rhesus monkeys that recovered from an attack of poliomyelitis with residual signs of the disease again became paralyzed when inoculated with the growth on blood agar plates of material obtained from the noses and throats of patients in the acute stage of measles. When the spinal cords of such animals were examined microscopically, there was no evidence of any acute inflammatory change such as is observed with poliomyelitis. Therefore, it is concluded that there was some other condition to account for these paralyses. It is inferred, although in no wise proved, that second attacks of poliomyelitis may be due not to the specific virus but to some other infection.

# EFFECT OF YEAST EXTRACT (VITAMIN B COMPLEX) ON GROWTH AND DEVELOPMENT OF PREMATURE INFANTS

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Cowgill, Rosenberg and Rogoff [1] observed in animal experimentation that in dogs subsisting on a diet deficient in vitamin B anhydremia rapidly developed. The observation that the administration of the vitamin B complex in appreciable amounts along with subcutaneous clysis results in definite retention of fluids in the body gave us a clue to the use of the vitamin B complex in the feeding of premature infants. In the treatment of marasmic infants who present evidences of dehydration, it is rather common practice to inject large amounts of fluids, but often with poor results. In the light of our present knowledge, it appears possible that in certain cases this practice may be really harmful unless the vitamin B complex is given at the same time.

Hoobler [2] found in many infants a syndrome which he described as indicative of a lack of antineuritic vitamins. The features of the symptom complex are anorexia, a strange, plaintive cry and a certain type of stiffness of arms, legs and neck believed to be similar to the spastic condition noticed in animals suffering from vitamin B deficiency. This condition is readily alleviated by the ingestion of sufficient amounts of the vitamin B complex.

Recently a number of investigators have called attention to the fact that the vitamin B complex, more particularly the antineuritic $B_1$ factor,

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Read before the Pediatric Section, Kings County Medical Society, and Academy of Medicine of Brooklyn, April 20, 1938.

Drs. Lichterman and Knoll are resident pediatricians at Beth-El Hospital: Dr. Kurland is resident obstetrician at Brooklyn Women's Hospital.

1. Cowgill, G. R.; Rosenberg, H. A., and Rogoff, J.: Am. J. Physiol. **95**: 589-594 (Nov.) 1931.

2. Hoobler, B. R.: Symptomatology of Vitamin B Deficiency in Infants. J. A. M. A. **91**:307-310 (Aug. 4) 1928.

may be present in too low concentration in cow's milk as well as in human milk for the optimal well-being of the infant. In the process of sterilization the $B_1$ factor may be further decreased, for it has been shown to be heat labile, the degree of destruction being influenced by the temperature to which the milk is heated and the duration of exposure to air during the heating. The processes used in evaporating milk as well as in drying it by the spray method have been shown to result in considerable destruction of the vitamin. Daniels and Brooks [3] and Daniels and White [4] reported that even the process of pasteurization results in some destruction of vitamin B.

Morgan and Barry [5] have shown that a shortage of vitamin B can be a factor limiting the growth of children. This observation probably has a great deal of significance, as our study was made on children of low income classes. Insufficient intake of the vitamin B complex during pregnancy is an important factor in prematurity. Clausen [6] stated that mothers whose diets are deficient in vitamin B are more likely to give birth to premature infants than those given a well balanced diet. Hess [7] showed that many marasmic infants had their interest in food and the urge to eat increased by the administration of vitamin B. Stucky and Rose [8] stated that the anhydremia noted in certain marasmic infants has its origin, in the last analysis, in a shortage of vitamin B. Thus if there is any question as to the adequacy of the intake of the vitamin B complex during pregnancy, the vitamin should be administered to the newborn infant.

An interesting experience we had with a premature infant who began to gain only after the administration of a yeast extract (vitamin B complex) pointed the way for further investigation of vitamin B in the infant dietary.

A boy weighing 1 pound and 12 ounces (787.5 Gm.) and 28 cm. in length was born after a six and a half month pregnancy at the Brooklyn Women's Hospital on March 4, 1936. The parent's history disclosed nothing unusual. The mother was a well developed woman who previously had given birth to two children at full term. There was no history of tuberculosis. The Wassermann reaction was negative. The infant was placed in an incubator for seven weeks. Clysis was given

3. Daniels, A. L., and Brooks, L.: Proc. Soc. Exper. Biol. & Med. **25**:161-163 (Dec.) 1927.

4. Daniels, A. L., and White, R. B.: Proc. Soc. Exper. Biol. & Med. **27**: 760-763 (May) 1930.

5. Morgan, A. F., and Barry, M. M.: Underweight Children, Am. J. Dis. Child. **39**:935-947 (May) 1930.

6. Clausen, S. W.: Nutrition and Infection, J. A. M. A. **104**:793-798 (March 9) 1935.

7. Hess, A. F.: Therapeutic Value of Yeast, Am. J. Dis. Child. **13**:98-109 (Jan.) 1917.

8. Stucky, C. J., and Rose, W. B.: Am. J. Physiol. **89**:1-17 (June) 1929.

from the second to the seventh week, the daily injection consisting of 40 cc. of 10 per cent dextrose in a physiologic solution of sodium chloride. Breast milk was given from the start, 2 to 6 dropperfuls being administered hourly for two weeks. When the supply of breast milk was exhausted, the infant was given evaporated milk and a dextrin-maltose-dextrose carbohydrate. This formula was gradually increased, but there was no change in weight until the beginning of the fourth week, when the infant was given a teaspoonful of yeast extract (vitamin B complex) twice daily in orange juice. The output of urine gradually came down to 160 Gm. per day, while the weight rose from 1 pound and 12 ounces to over 5 pounds (2,268 Gm.) by the end of the fifteenth week (chart 1).

## MATERIAL AND METHODS

The results obtained in this case with the use of yeast extract (vitamin B complex) were made the basis for a plan of study of premature infants, which was begun in the fall of 1936 and followed through to the fall of 1937. During

TABLE 1.—*Classification of Infants Born in Beth-El Hospital and in Brooklyn Women's Hospital from October 1936 to September 1937, Inclusive*

| | Newborn Infants | Stillbirths | Premature Infants | Premature Twins | Premature Deaths |
|---|---|---|---|---|---|
| October | 253 | 15 | 6 | 0 | 4 |
| November | 218 | 6 | 8 | 0 | 1 |
| December | 206 | 9 | 8 | 1 | 1* |
| January | 215 | 8 | 6 | 0 | 0 |
| February | 188 | 4 | 11 | 0 | 1 |
| March | 239 | 11 | 6 | 0 | 1 |
| April | 235 | 7 | 9 | 0 | 3 |
| May | 212 | 5 | 8 | 0 | 3 |
| June | 197 | 7 | 5 | 0 | 2 |
| July | 201 | 3 | 2 | 0 | 1 |
| August | 209 | 9 | 3 | 0 | 1 |
| September | 206 | 5 | 6 | 0 | 2 |
| Total | 2,579 | 89 | 78 | 1 | 20 |
| Percentage | | 2.5 | 3.3 | | 25† |

* One of premature twins.
† Slightly more than 25 per cent of the premature infants died.

the year 1936-1937, 2,579 infants were born at the two hospitals (table 1). This table shows that 89 (2.5 per cent) were stillborn and that 78 (3.3 per cent) were premature (of which 20 died). The time of births and deaths was also tabulated. Fifty-eight premature infants were available for our clinical study.

A group of 52 premature infants from the year 1935-1936 were used as a control.

The standardized routine care for premature infants in both hospitals provides the best means of maintenance of body heat, individual nursing care, proper feeding and isolation. A premature infant is received in a warm sterile blanket; after being weighed in the delivery room he is brought to the nursery for a quick oil bath and a cotton jacket and is then placed in the incubator. The incubator is regulated for temperature but not for humidity. When no incubator is available, a bassinet is kept at body temperature by means of hot water bottles or an electric pad, or an incubator is improvised as described by Dembo.[9]

Individual nursing care is important in order that temperature changes may be checked and oxygen or carbon dioxide may be administered when necessary (cyanosis may set in at any time during the first few days). When frequent

9. Dembo, L. H.: Arch. Pediat. **39**:269-270 (April) 1922.

change of diapers was necessary, these changes were accomplished in the incubator, preferably just before feeding. Oil baths were given twice daily.

The premature infants were fed individually. Although there were no definite rules, weight was the most important factor in determining the feeding. Those weighing less than 600 Gm. were given breast milk by a medicine dropper or by gavage and were slowly transferred to the Breck feeder. When they reached a weight of approximately 2,000 Gm., they were fed from bottles with medium-sized nipples. Breast milk was used to some extent in feeding both the control group and the observed group, but in the majority of cases the formula consisted of modified evaporated milk. The caloric intake was between 60 and 90 calories per pound of body weight, starting with the lower figure and gradually increasing to the higher. We began by giving from 1 to 4 drachms (3.7 to 15.8 cc.) every

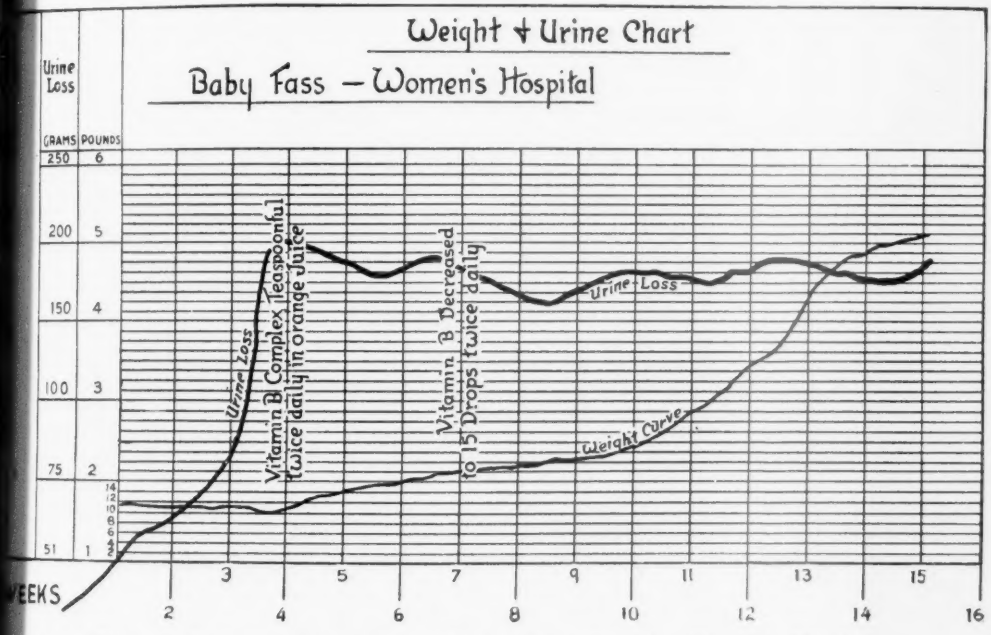


Chart 1.—Data on a baby born in March 1936 at Brooklyn Women's Hospital. The weight at birth was 1 pound and 12 ounces (787.5 Gm.) and the length 28 cm. The light line indicates weight and the heavy line excretion of urine. During the first week of life the intake was approximately 120 cc. daily; second week, 280 cc.; third week, 320 cc.; fourth week, 360 cc.; fifth week, 360 cc.; tenth week, 450 cc., and fourteenth week, 700 cc. For five weeks, from the second to the seventh week, a clysis of 40 cc. was given daily.

hour, the amount and the time intervals being gradually increased. After the first ten days, the infants were usually given 1 ounce (29.6 cc.) every two hours or more as the condition of the child permitted.

Every precaution was taken to isolate the premature infants in order to avoid infection. They were kept away from the general nursery and were handled only by masked and gowned nurses who were daily examined for infection of the upper respiratory tract. There was careful supervision of formulas, bottles

and nipples, and all contacts with the infants were limited to physicians and nurses. In premature infants we have frequently seen bronchial pneumonia without elevation of temperature and parenteral infections which are difficult to check. Thus isolation is a primary principle in their care.

The standardized routine just described was used for both the control group of 52 babies during the years 1935-1936 and the observed group of 58 infants during the years 1936-1937. As far as could be managed, the only variable factor between the control group and the observed group was the administration of yeast extract (vitamin B complex).[10] Because of the numerous fractions of vitamin B thus far identified, a liquid yeast extract containing the entire B complex in its natural form was used in preference to any of the synthetic preparations. The

TABLE 2.—*Length of Time Required to Show Definite Gain in Weight of Fifty-Eight Premature Infants Given Yeast Extract (Vitamin B Complex)* *

| | Gain in Weight, Oz. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Original Weight, Gm. | ½ Wk. | 1 Wk. | 1½ Wk. | 2 Wk. | 2½ Wk. | 3 Wk. | 3½ Wk. | 4 Wk. | 4½ Wk. | 5 Wk. |
| 1,000 or under | .. | .. | .. | .. | .. | .. | .. | 1 | .. | .. |
| 1,001 to 1,500 | .. | .. | 1 | 1 | 1 | .. | .. | .. | .. | .. |
| 1,501 to 2,000 | .. | .. | 3 | 4 | 2 | .. | .. | .. | .. | .. |
| 2,001 to 2,500 | 4 | 28 | 6 | 1 | 4 | 2 | .. | .. | .. | .. |
| Total | 4 | 28 | 10 | 6 | 7 | 2 | | 1 | | |
| Percentage gained | 6.89 | 48.27 | 17.24 | 10.34 | 12.06 | 3.44 | | 1.72 | | |

* These infants showed an average gain of from ½ to 1½ ounces (14.2 to 42.5 Gm.) daily from the day increase began.

TABLE 3.—*Length of Time Required to Show Definite Gain in Weight of Fifty-Two Premature Infants Not Receiving Yeast Extract (Vitamin B Complex)**

| | Gain in Weight, Oz. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Original Weight, Gm. | ½ Wk. | 1 Wk. | 1½ Wk. | 2 Wk. | 2½ Wk. | 3 Wk. | 3½ Wk. | 4 Wk. | 4½ Wk. | 5 Wk. |
| 1,000 or under | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| 1,001 to 1,500 | .. | .. | .. | .. | .. | 1 | .. | 1 | 1 | .. |
| 1,501 to 2,000 | .. | .. | 4 | .. | 3 | 2 | 5 | 6 | 3 | .. |
| 2,001 to 2,500 | .. | 4 | 2 | 7 | 5 | 4 | 2 | .. | 2 | .. |
| Total | .. | 4 | 6 | 7 | 8 | 7 | 7 | 7 | 6 | |
| Percentage gained | | 7.69 | 11.53 | 13.46 | 15.38 | 13.46 | 13.46 | 13.46 | 11.53 | |

* These infants started to gain on the average much later than those given yeast extract and gained at a much slower rate, the increase averaging about ¼ to ½ ounce (7.1 to 14.2 Gm.) daily or every other day.

yeast extract had a potency of 100 international $B_1$ (B) units and 40 Sherman-Bourquin $B_2$ (G) units per teaspoonful (4 cc.). This preparation was used for the latter half of the infants included in the observed group. For the first half of the observed group, the preparation used was the one available at that time, which had only approximately half of this potency. In the beginning our dosage was not guided by any hard and fast rules. To some of the premature infants we routinely gave a teaspoonful twice daily in orange juice until we saw an appreciable gain in weight. Then the dosage was decreased to approximately 15 drops given twice daily in orange juice. At no time did we notice any gastrointestinal disturbances. All infants were given a 40 cc. clysis of 10 per cent

10. Kinney's yeast extract, which contains the vitamin B complex, was supplied by Scientific Sugars Co.

dextrose in a physiologic solution of sodium chloride or 40 cc. of a physiologic solution of sodium chloride alone twenty-four hours after birth. The approximate intake of these infants was for the first week from 120 to 150 cc. daily, for the second week from 280 to 300 cc. daily, for the fourth week from 360 to 400 cc. daily and for the fifth week 400 cc. daily.

## RESULTS

Tables 2 and 3 present a comparison of the two groups with regard to the period after birth before definite gains in weight were made. In table 2 are listed the premature infants given the yeast extract according to their weight and the length of time after birth before they began

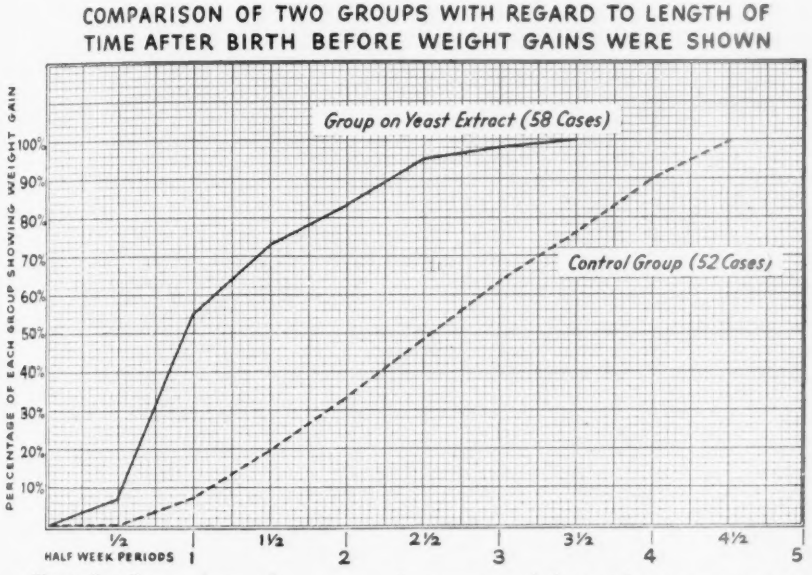


Chart 2.—Comparison of a group of premature infants given yeast extract and a group not given extract with regard to gain in weight.

to gain. Table 3 gives the same information for the control group of premature infants that did not receive the yeast extract. It is interesting that whereas in the control group no infants began to gain in the first part of the first week, there were 4 infants of the group who were receiving the yeast extract that did show a gain in that period. Twenty-eight of those who received the yeast extract showed definite gains in the last half of the first week, as against only 4 of the control group who showed a gain in that period. Of the 58 infants that received the yeast extract, only 1 had failed to show a gain at the end of the third week, whereas of the control group, who received no yeast extract, 20 had failed to show a gain at the end of this period. Chart 2 gives these data in graphic form. Time is divided into half-week periods

along the bottom of the chart. The percentage of each group showing weight gains at the end of the half-week periods is represented vertically on the graph. As seen in the graph, at the end of the first week 55 per cent of the group receiving yeast extract showed definite gains in weight, whereas less than 8 per cent of the control group showed gain at the end of this period. Ninety-five per cent of those receiving yeast extract showed gains in weight at the end of two and one-half weeks, whereas only approximately 48 per cent of the control group showed gains at the end of this period.

Because of the wide variation in birth weights, no attempt was made to strike a comparison between the two groups of the average gains in weight. However, tables 4 and 5 make a comparison of the

TABLE 4.—*Weight at Three Months Compared With Weight at Birth of Premature Infants Given Yeast Extract (Vitamin B Complex)*

| Weight After 3 Months | Infants' Weight at Birth | |
|---|---|---|
| | Under 1,500 Gm. | 1,501-2,000 Gm. |
| Double birth weight | 0 | 5 |
| Triple birth weight | 0 | 36 |
| Four times birth weight | 2 | 11 |
| Five times birth weight | 1 | 3 |

TABLE 5.—*Weight at Three Months Compared With Weight at Birth of Premature Infants Not Given Yeast Extract (Vitamin B Complex)*

| Weight After 3 Months | Infants' Weight at Birth | |
|---|---|---|
| | Under 1,500 Gm. | 1,501-2,000 Gm. |
| Double birth weight | 1 | 31 |
| Triple birth weight | 2 | 18 |
| Four times birth weight | 0 | 0 |
| Five times birth weight | 0 | 0 |

weights of the two groups at the age of 3 months. Of those having a birth weight of 1,500 Gm. or over and receiving the yeast extract, 3 weighed five times their birth weight at 3 months; 11 weighed 4 times their birth weight; 36 tripled their birth weight, and 5 doubled their birth weight. Of those of the control group who weighed 1,500 Gm. or over at birth, none weighed five times the birth weight at 3 months, nor did any weigh 4 times the birth weight. Only 18 tripled and 31 doubled the birth weight. In general, it may be said that those given yeast extract began to gain weight much sooner and gained at a faster rate than those who received no yeast extract.

## SUMMARY

Of 2,579 newborn infants delivered in two hospitals in the year 1936-1937, 78 were premature; of these 20 died, leaving 58 for clinical

study. In addition to the standardized routine procedure for caring for premature infants, this group of 58 were given varying doses of yeast extract (vitamin B complex). The period required to show gain and the percentage of gain of this group after three months were compared with those of a control group of 52 infants who received no yeast extract.

1. Infants receiving yeast extract showed gains in weight much sooner than those not receiving this preparation. Of the group receiving yeast extract 55 per cent began to gain during the first week of life, whereas less than 8 per cent of the control group showed a gain during the first week. Ninety-five per cent of those receiving yeast extract showed gains at the age of 2½ weeks, whereas only approximately 48 per cent of the control group showed gains at the end of this period.

2. Infants with birth weights under 1,500 Gm. who were given yeast extract attained four or five times their birth weight at the age of 3 months, as compared with those not given yeast extract, who only doubled or tripled their weight at this age. Of those having a birth weight over 1,500 Gm. twice as many of those given yeast extract tripled their weight as of those without the extract, and many of those given the yeast extract quadrupled their weight. Three infants given yeast extract showed a gain of five times their birth weight at 3 months.

3. No gastrointestinal disturbances accompanied the administration of yeast extract.

# GROWTH IN CHILDREN WITH MONGOLISM

## A FOUR YEAR STUDY OF EIGHT PATIENTS

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Mongolism is a condition recognizable at birth; it is characterized by generalized skeletal somatic and by mental retardation.

While Sequin, of France, and Lombroso,[1] of Italy, mentioned this condition in some early articles, it remained for Down,[2] in 1866, to describe mongolism; he gave it this name because the features of the patients resemble those of the Kalmuc and Tartar tribes.

Muir,[3] in 1903, mentioned two German and five American references and stated that mongolism seemed to be confined to the Caucasian race. This view was generally accepted until about 1922, when reports were published of mongolism in Chinese children by Demuth[4] and Trumpeer.[5] Since that time many cases of mongolism have been reported as occurring in Chinese, Japanese, Jews, Hindus, Negroes, American Indians[6] and others.

Cases have been reported from almost every country of the world. The condition seems to be universal as regards race.

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1. Lombroso, cited by Brousseau, K.: Mongolism, Baltimore, Williams & Wilkins Company, 1928.

2. Down, J. L. H.: Observations on Ethnic Classification of Idiots, Clin. Lect. & Rep. London Hosp. **3**:259, 1866.

3. Muir, J.: An Analysis of Twenty-Six Cases of Mongolism, Arch. Pediat. **20**:161, 1903.

4. Demuth, F.: Mongoloide Idiotie bei einem Mongolen, Ztschr. f. Kinderh. **33**:110 (July) 1922.

5. Trumpeer, H.: Mongolian Idiocy in a Chinese Boy, J. A. M. A. **79**: 14 (July 21) 1922.

6. Bleyer, A.: Mongolism in a North American Indian, J. Missouri M. A. **33**:13 (Jan.) 1936.

## FREQUENCY

Bleyer[7] reported 115 (14.6 per cent) patients with mongolism among 777 mentally defective children of a group of almost 50,000 children admitted to the Washington University Dispensary. According to the United States Bureau of Census, there are 153 mentally defective persons per hundred thousand of the population. Bleyer estimated that should the proportion 14.6 per cent, found in patients admitted to the Washington University Dispensary, be at all representative, it would indicate that there are approximately 28,000 persons with mongolism in the United States, one sixth or one fifth of whom are in institutions and the remainder, about 20,000, at large.

## ETIOLOGY

The cause of mongolism is still unknown. The inhibiting influences which produce this type of abnormality are operative during fetal life and may have their beginning during embryonic development. The syndrome is clearcut; there can be no mistake in the diagnosis. There is hardly any other condition in which the signs and symptoms occur with such amazing uniformity. Whenever a syndrome so definite as mongolism exists in a large number of persons of most, if not all, races, there must be some definite causative factor or factors.

There is some difference of opinion as to whether certain endocrine glands, especially the thyroid, are involved in mongolism. Some authors have noted at autopsy such pathologic conditions in the thyroid as extensive sclerosis, atrophy, interstitial proliferation, colloid degeneration and hemorrhagic areas. Gordon[8] reported 2 cases in which he observed changes in the thyroid, pituitary, adrenals, thymus, pineal body and ovaries on postmortem examination.

Among other ideas and theories as to the cause of mongolism may be mentioned those of (*a*) reversion to a propithecanthropoid ancestor, an idea not far from ridiculous; (*b*) heredity, which has practically no evidence to substantiate it; (*c*) some definite disturbance in the germ cells, which would have to be the same in each instance because of the similarity of the syndrome in all afflicted persons; (*d*) advanced age of the parents, especially the mother, a theory not supported by evidence; (*e*) a syphilitic origin, which is disproved by serologic tests. There are other theories as to the origin of this condition, all engendered by a lack of knowledge concerning the true cause.

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7. Bleyer, A.: The Frequency of Mongoloid Imbecility, Am. J. Dis. Child. **44**:503 (Sept.) 1932.

8. Gordon, M. B.: Morphological Changes in the Endocrine Glands in Mongolian Idiocy with Report of Two Cases, Endocrinology **14**:1 (Jan.-Feb.) 1930.

### DIAGNOSTIC SIGNS

The similarity of appearance of the patients is striking. The physiognomy shows great likeness to that of the Mongolian races. The skull is small and round and the occiput flat. The fontanels and sutures remain open abnormally long; the lower jaw as a rule projects; the zygomatic arches are prominent, and the forehead is low and flat. The mouth is small and is held open, dentition is delayed, and the teeth are badly formed and irregularly placed. The tongue is not essentially large, is dry and fissured, has prominent papillae and lies between the separated rows of teeth. The palatal arches are high. The palpebral fissures are small, oblique and slitlike and show epicanthus. Conjunctivitis is frequent. Strabismus or nystagmus is often present. The nose is small and button-like, the bridge is sunken, and the nares are tilted upward and stand open so that one can look directly into them. The ears may be small and stand back or they may be cupped and flaring.

The face is expressionless and vacant only in the first year of life; afterward it is gay, comical and imbecilic.

The appearance of the bony nuclei may be slightly delayed in some cases; in others, ossification is normal. The skeleton is well proportioned, but growth in height is somewhat stunted. The hands are short and chubby, the fingers are short, the middle phalanges of the little fingers are shortened and the distal phalanges are atrophied and curve inward. The thumbs are short. Each great toe is widely separated from the next digit. The joints are hyperextensile. The hair is soft and silky, and the skin is smooth, moist, elastic and redundant. The genitalia are poorly developed; frequently there is delay in descent of the testicles, and though function may later be normal, libido is slight.

Persons with mongolism usually are short lived and are said to be subject to tuberculosis. Mental development is delayed; it may be of any degree up to imbecility but is never above that level. The patients are lively, and their attention is fixed with difficulty. They are mimics, show considerable power of imitation and pose readily. It is questionable whether thyroid medication is of much benefit.

### STUDY OF EIGHT PERSONS WITH MONGOLISM

This study was conducted by treating and observing 8 afflicted persons, 5 at the St. Louis Training School for Mentally Defective Children and 3 private patients, for four years. Their ages at the beginning of treatment ranged from 2 years and 9 months to 7 years and 4 months.

The points of interest to be observed were as follows:

1. The effect of an anterior pituitary extract containing the growth hormone in children with mongolism for one year.

2. The effect of the anterior pituitary extract and desiccated thyroid on growth and increase of weight in children with mongolism during the second year.

3. Comparison of increase in height and in weight during a two year period, throughout which no treatment was administered, with increase during the two year period of treatment.

4. Comparison of increase in height and weight of children with mongolism with those of normal children of the same age.

5. Comparison of the actual height and weight of children with mongolism with the average height and weight of normal children of the same age.

6. Comparison of increase in height and weight of treated children with mongolism with that of 5 untreated children with mongolism of approximately the same age.

TABLE 1.—*Miscellaneous Data on Eight Children With Mongolism*

| Patient | Age | Order of Birth | Number of Children in Family | Age of Mother at Birth of Child, Years | Age of Father at Birth of Child, Years | Osseous Development, Years |
|---|---|---|---|---|---|---|
| 1 | 6 yr., 1 mo. | 2 | 2 | 33 | 31 | 4 |
| 2 | 4 yr., 7 mo. | 3 | 3 | 36 | 36 | 2 |
| 3 | 2 yr., 9 mo. | 4 | 4 | 43 | 41 | 3 |
| 4 | 2 yr., 10 mo. | 1 | 2 | 25 | 33 | 2 |
| 5 | 5 yr. | 5 | 5 | 43 | 55 | 3 |
| 6 | 5 yr., 11 mo. | 11 | 11 | 42 | 43 | 3 |
| 7 | 7 yr., 4 mo. | 2 | 2 | 21 | 29 | 5 |
| 8 | 6 yr., 2 mo. | 3 | 3 | 32 | 27 | 5 |

7. The effect of treatment on the mental age and the intelligence quotient in children with mongolism.

Table 1 gives the ages of these patients at the beginning of treatment, their order of birth, the number of children in the family, the ages of the mother and father at the time of birth of the afflicted children and their approximate degree of osseous development.

In only 1 instance, that of patient 6, was the child the last born in a family of eleven. Patient 4 was first in order of birth, 1 and 7 were second, 2 and 8 were third and the remaining 2 were fourth and fifth, respectively. It is interesting to note that in only 1 instance, that of patient 4, did a mother have another child after the birth of one with mongolism. The reason given for this is fear of a similar occurrence in future pregnancies. Only one who has had intimate contact with the family can understand the mental distress suffered by the parents of these children. Almost all people have a feeling of ances-

tral pride, and the birth of a child with mongolism is a severe blow, regardless of the fact that heredity probably plays no role in the causation of this condition. In none of the families does the ancestry for three generations or more indicate the presence of mental disease or mongolism. The father of patient 4 is a graduate of Princeton, and the mother, of Vassar. The parents of some of the other children are college graduates.

The blood counts were within normal limits, and the Wassermann and Kahn reactions were negative. Osseous development, as judged by a general survey of the skeleton, showed moderate retardation except in patient 3, in whom it was normal. All the children had most of the signs and evidences of mongolism.

### MENTAL AGE AND INTELLIGENCE

The abnormalities of the nervous system were numerous and extremely varied.

Many investigators have found that in persons with mongolism the brain is always below normal in size and weight and that there is a deficiency in the number and development of the convulutions, with diffuse cortical changes.[9]

The American Association on Mental Deficiency has classified mental deficiency into three grades, on the basis of the Binet scale: moronism, imbecility and idiocy. Persons having a mental age of from 8 to 12 years are designated as morons, those with an age of from 4 to 7 years as imbeciles and those who do not progress beyond 3 years as idiots.

Interesting data in table 2 are those pertaining to the mental ages and the intelligence quotients of these patients over a period of two years. The mental age and the intelligence quotients were determined at the beginning of the treatment, after one year and after two years. In each instance these determinations were made by different persons; two were well known psychiatrists, and the third was a postgraduate student of psychiatry. In no instance did any of these psychiatrists study the determinations of previous investigators.

While there was slight improvement in the mental age in most of the patients at the end of the two year period of treatment, it will be noted that none advanced beyond the 3 year mental age limit, that for idiocy. There was no improvement in the intelligence quotient, the slight variations being closely within the normal variation of error.

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9. Davidoff, L. M.: The Brain in Mongolian Idiocy: A Report of Ten Cases, Arch. Neurol. & Psychiat. **20**:1229 (Dec.) 1928.

TABLE 2.—*Changes in Eight Children With Mongolism Treated for Two Years* *

| Patient | | Before Treatment: Age | | Before Treatment: Height, In. | Before Treatment: Weight, Lb. | Before Treatment: Mental Age | | Before Treatment: Intelligence Quotient, % | After One Year: Height, In. | After One Year: Weight, Lb. | After One Year: Intelligence Quotient, % | After Two Years: Height, In. | After Two Years: Weight, Lb. | After Two Years: Mental Age | | After Two Years: Intelligence Quotient, % | Summary of Change in 2 Years: Height, In. | Summary of Change in 2 Years: Weight, Lb. | Summary of Change in 2 Years: Mental Age, Mo. | Summary of Change in 2 Years: Intelligence Quotient, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | No. | Yr. | Mo. | | | Yr. | Mo. | | | | | | | Yr. | Mo. | | | | | |
| P. W. | 1 | 6 | 1 | 39 | 33 | 1 | 10 | 30 | 41¼ | 37½ | 37 | 43 | 40½ | 3 | .. | 38 | 4 | 7½ | +14 | +8 |
| B. G. | 2 | 4 | 7 | 36¾ | 31 | 2 | .. | 42 | 39¾ | 36¾ | 44 | 42½ | 42¾ | 2 | 10 | 44 | 5¾ | 11¾ | +10 | +2 |
| F. S. | 3 | 2 | 9 | 35½ | 28 | 1 | 8 | 58 | 38 | 34¼ | 65 | 40¾ | 40¼ | 1 | 8 | 56 | 5¼ | 12¼ | 0 | −2 |
| A. B. | 4 | 2 | 10 | 33½ | 25¼ | 1 | .. | 35 | 35 | 27½ | 30 | 38½ | 33 | 1 | 7 | 33 | 5 | 7¾ | + 9 | −2 |
| A. K. | 5 | 5 | .. | 37½ | 34 | 1 | 11 | 38 | 38¾ | 36½ | 33 | 41 | 44 | 2 | .. | 30 | 3½ | 10 | + 1 | −8 |
| F. R. | 6 | 5 | 11 | 35½ | 38 | 1 | 8 | 28 | 40¾ | 35 | 29 | 41¾ | 39 | 2 | .. | 26 | 6¼ | 1 | + 4 | −2 |
| R. R. | 7 | 7 | 4 | 42¼ | 36 | 2 | 4 | 30 | 43½ | 37 | 26 | 45 | 41 | 2 | 11 | 30 | 2¾ | 5 | + 7 | 0 |
| A. M. | 8 | 6 | 2 | 40¾ | 36¼ | 2 | .. | 32 | 42¼ | 38 | 30 | 43½ | 48 | 2 | 6 | 30 | 2¾ | 11¾ | + 6 | −2 |

* During both years 2 cc. (10 rat units of growth factor per cubic centimeter) of an extract of the anterior lobe of the pituitary gland was given intramuscularly every other day; during the second year 1 grain (0.06 Gm.) of desiccated thyroid was given daily.

TABLE 3.—*Summary of Increase in Height and Weight* * *During the Four Year Period* †

| Patient | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | Average Increase per Child | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 6 yr. 1 mo. | | 4 yr. 7 mo. | | 2 yr. 9 mo. | | 2 yr. 10 mo. | | 5 yr. | | 5 yr. 11 mo. | | 7 yr. 4 mo. | | 6 yr. 2 mo. | | | |
| | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight |
| Growth factor, 1 year | 2.25 | 4.50 | 3.00 | 5.75 | 2.50 | 6.25 | 1.50 | 2.25 | 1.25 | 2.50 | 5.25 | 3.00 | 1.25 | 1.00 | 1.50 | 1.75 | 2.31 | 2.63 |
| Normal expectancy | 2.20 | 4.70 | 2.60 | 4.00 | 2.90 | 4.10 | 2.90 | 4.10 | 2.30 | 4.20 | 2.20 | 4.70 | 2.00 | 5.00 | 2.20 | 4.70 | 2.41 | 4.44 |
| Growth factor and thyroid, 1 year | 1.75 | 3.00 | 2.75 | 6.00 | 2.75 | 6.00 | 3.50 | 5.50 | 2.25 | 7.50 | 1.00 | 4.00 | 1.50 | 4.00 | 1.25 | 10.00 | 2.09 | 5.75 |
| Normal expectancy | 2.10 | 4.70 | 2.40 | 4.40 | 2.50 | 3.90 | 2.50 | 3.90 | 2.20 | 4.60 | 3.20 | 4.70 | 2.00 | 5.80 | 2.90 | 4.70 | 2.54 | 4.59 |
| Total increase on treatment, 2 years | 4.00 | 7.50 | 5.75 | 11.75 | 5.25 | 12.25 | 5.00 | 7.75 | 3.50 | 10.00 | 6.25 | 1.00 | 2.75 | 5.00 | 2.75 | 11.75 | 4.40 | 8.38 |
| Normal expectancy | 4.30 | 9.40 | 5.00 | 8.40 | 5.40 | 8.00 | 5.40 | 8.00 | 4.50 | 8.80 | 5.40 | 9.40 | 4.00 | 10.80 | 5.10 | 9.40 | 4.95 | 9.03 |
| Growth without treatment, 2 years | 4.00 | 8.50 | 5.75 | 19.25 | 3.25 | 2.50 | 3.50 | 5.00 | 4.00 | 10.50 | 2.75 | 7.50 | 7.75 | 15.75 | 3.75 | 10.00 | 4.34 | 9.88 |
| Normal expectancy | 4.00 | 11.50 | 4.25 | 7.40 | 4.50 | 8.90 | 4.50 | 8.90 | 4.00 | 10.10 | 4.50 | 11.60 | 4.50 | 16.10 | 3.50 | 11.60 | 4.22 | 10.75 |
| Total increase in 4 years | 8.00 | 16.00 | 11.50 | 31.00 | 8.75 | 14.75 | 8.50 | 12.75 | 7.50 | 20.50 | 9.00 | 8.50 | 10.50 | 20.75 | 6.50 | 21.75 | 8.78 | 18.26 |
| Normal expectancy | 8.30 | 20.90 | 9.25 | 15.80 | 9.90 | 16.90 | 9.90 | 16.90 | 8.50 | 18.90 | 9.90 | 21.00 | 8.50 | 26.90 | 8.60 | 21.00 | 9.17 | 19.78 |

* Height is expressed in inches and weight in pounds.
† Treatment was given for the first two years (footnote, table 2); none was given for the next two years.

GROWTH

Table 3 summarizes the increase in height and weight of these children over a four year period. Height and weight were determined before treatment, at the end of the first and of the second year of treatment and after the two year period of observation, during which no treatment was administered. The height and weight were compared with the average increment for normal children of the same age.

At the end of the first year the children with mongolism had an average increase in height of 2.31 inches (5.87 cm.) (average normal 2.41 inches [6.12 cm.]) and an average gain in weight of 2.63 pounds (1.19 Kg.) (average normal 4.44 pounds [2.01 Kg.]). During the second year, the average increase in height was 2.09 inches (5.31 cm.) (normal 2.54 inches [6.45 cm.]), and the average gain in weight was 5.75 pounds (2.61 Kg.) (normal 4.59 pounds [2.08 Kg.]). During the third and fourth years without treatment the average increase in height was 4.34 inches (11.02 cm.) (normal 4.22 inches [10.72 cm.]) and in weight 9.88 pounds (4.48 Kg.) normal 10.75 pounds [4.57 Kg.]). The average increase in height for the two year period of treatment was 4.4 inches (11.18 cm.), as compared with 4.34 inches (11.02 cm.) for the two year period of no treatment. The average gain in weight for the same period was 8.38 pounds (3.8 Kg.) (normal 9.88 pounds [4.48 Kg.]).

The average increase in height in the children with mongolism over the four year period was 8.78 inches (22.3 cm.), as compared with 9.17 inches (23.29 cm.) for normal children of the same age. The average increase in weight for four years was 18.26 pounds (8.28 Kg.) (normal 19.78 pounds [8.97 Kg.]).

To summarize the increment in growth and weight:

The average difference in increase of height during the two years of treatment and the two years of no treatment was 0.06 inch (0.15 cm.).

The average difference of increase in weight during two years' treatment and the two years of no treatment was 1.5 pounds (0.68 Kg.).

The average difference of increase in height of the treated children with mongolism and of normal children of the same age was 0.39 inch (0.99 cm.).

The average difference of increase in weight of the treated children with mongolism and of normal children of the same age over a four year period was 1.52 pounds (0.69 Kg.).

It is evident that the average increment in height of the treated children with mongolism was equal to that of normal children of the same age over a period of four years (minus 0.39 inch [0.99 cm.]).

The average growth of the children with mongolism was almost exactly equal during the two year period of treatment and during that of no treatment (difference 0.06 inch [0.15 cm.]).

### COMPARISON OF ACTUAL INCREMENTS IN HEIGHT AND WEIGHT WITH AVERAGE FOR NORMAL CHILDREN OF SAME AGE

Table 4 compares the actual height and weight of the treated children with mongolism with the height and weight of normal children of the same age over a four year period.

It is seen that at the beginning of treatment of the patients their average height was 4.75 inches (12.06 cm.) less than that of normal children of the same age and their average weight 6.98 pounds (3.17 Kg.) less.

It is a surprising fact that over a four year period the treated children with mongolism maintained an increment in growth and weight equal to that of normal children of the same age. At the beginning of treatment, the patients were 4.75 inches (12.06 cm.) under the average normal for height. While the growth in height for the treated children over the four year period was 8.78 inches (22.3 cm.), at the end of four years they were still 4.94 inches (12.55 cm.) under the height of normal children of the same age. This indicates that these afflicted children grew as rapidly as average normal children do at these ages but that their stature was approximately 5 inches (12.7 cm.) below that of normal children of the same age. In other words, they were dwarfed.

### INCREASE IN HEIGHT AND WEIGHT OF FIVE UNTREATED CHILDREN WITH MONGOLISM (CONTROLS) OVER A FOUR YEAR PERIOD

Through the assistance of Dr. Ransom A. Greene, Superintendent of the Walter E. Fernald State School, Waverly, Mass., we were supplied with data on the growth and weight of a group of untreated children with mongolism. In this group were 5 children of approximately the same ages as those of the patients whom we had been observing for four years.

It is interesting to note (table 5) that the control group of 5 untreated patients with mongolism had an average growth in height of 8.4 inches (21.34 cm.) and an average increase in weight of 14.9 pounds (6.8 Kg.) over a four year period. Their growth was only 0.38 inch (0.97 cm.) less than that of the treated patients and 0.77 inch (1.96 cm.) less than that of normal children of the same age over a four year period. The average increase in weight was only slightly less.

### CONCLUSIONS

Eight children with mongolism treated with an anterior pituitary extract containing the growth factor and with desiccated thyroid grew in height and weight approximately as did normal children of the same age over a four year period.

TABLE 4.—*Comparison of Actual Increment in Height and Weight* of Patients With Mongolism With Average Increment of Normal Children of Same Age*

| Patient... | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | Average Height and Weight | | Average Variation in | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age..... | 6 yr. 1 mo. | | 4 yr. 7 mo. | | 2 yr. 9 mo. | | 2 yr. 10 mo. | | 5 yr. | | 5 yr. 11 mo. | | 7 yr. 4 mo. | | 6 yr. 2 mo. | | | | | |
| | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight |
| Beginning of treatment..... | 39.00 | 33.00 | 36.75 | 31.00 | 35.50 | 28.00 | 33.50 | 25.25 | 37.50 | 34.00 | 35.50 | 38.00 | 42.25 | 36.00 | 40.75 | 36.25 | 37.59 | 32.70 | | |
| Average normal.. | 45.00 | 43.90 | 40.90 | 36.00 | 36.90 | 32.30 | 36.90 | 32.30 | 42.70 | 39.70 | 45.00 | 43.90 | 46.30 | 49.30 | 45.00 | 43.90 | 42.34 | 39.68 | 4.75 | 6.98 |
| End of 1st year.. | 41.25 | 37.50 | 39.75 | 39.75 | 38.00 | 34.25 | 35.00 | 27.50 | 38.75 | 36.50 | 40.75 | 35.00 | 43.50 | 37.00 | 42.25 | 38.00 | 39.90 | 37.70 | | |
| Average normal.. | 47.50 | 48.60 | 43.40 | 40.00 | 40.20 | 37.50 | 40.20 | 37.50 | 45.00 | 43.90 | 47.20 | 38.60 | 48.20 | 54.30 | 47.50 | 48.60 | 44.90 | 44.80 | 5.00 | 7.10 |
| End of 2d year.. | 43.00 | 40.25 | 42.50 | 42.75 | 40.75 | 40.25 | 38.50 | 33.00 | 41.00 | 44.00 | 41.75 | 39.00 | 45.00 | 41.00 | 43.50 | 48.00 | 42.00 | 41.00 | | |
| Average normal.. | 49.20 | 53.30 | 45.70 | 44.40 | 42.90 | 41.60 | 42.90 | 41.60 | 47.20 | 48.60 | 49.20 | 53.30 | 50.10 | 60.10 | 49.20 | 53.30 | 47.00 | 49.50 | 5.00 | 8.50 |
| End of 4th year. | 47.00 | 49.00 | 48.25 | 62.00 | 44.25 | 42.75 | 42.00 | 38.00 | 45.00 | 54.50 | 44.50 | 46.50 | 53.00 | 56.75 | 47.25 | 58.00 | 46.40 | 50.94 | | |
| Average normal.. | 53.20 | 64.90 | 49.90 | 54.30 | 47.70 | 50.80 | 47.70 | 50.80 | 51.20 | 58.60 | 53.20 | 64.90 | 54.60 | 76.20 | 53.20 | 64.90 | 51.34 | 60.67 | 4.94 | 9.73 |

* Height is expressed in inches and weight in pounds.

TABLE 5.—*Increase in Height and Weight of Five Untreated Children With Mongolism (Controls) in Four Years**

| Patient..... | 1 | | 2 | | 3 | | 4 | | 5 | | Average Gain in Height and Weight for Group | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age..... | 1 yr. 1 mo. | | 4 yr. 8 mo. | | 4 yr. 10 mo. | | 5 yr. | | 5 yr. | | | |
| | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight | Height | Weight |
| Admission..... | 27.50 | 14.00 | 42.80 | 40.50 | 40.00 | 37.00 | 36.50 | 34.00 | 39.00 | 35.00 | 37.16 | 32.10 |
| After 4 years..... | 44.50 | 37.00 | 48.00 | 58.00 | 48.00 | 53.00 | 42.30 | 45.00 | 45.00 | 42.00 | 45.56 | 47.00 |
| Total increment of controls in 4 years..... | 17.00 | 23.00 | 5.20 | 17.50 | 8.00 | 16.00 | 5.80 | 11.00 | 6.00 | 7.00 | 8.40 | 14.90 |
| Total increment of treated children in 4 years†..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 8.78 | 18.26 |
| Total increment of normal children of same age in 4 years..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 9.17 | 19.78 |

* Height is expressed in inches and weight in pounds.
† Treated for two years, then no treatment given for two years (footnote, table 2).

Five untreated children with mongolism increased in height and weight over a four year period at a rate approximately equal to that of normal children of the same age.

The stature of the children with mongolism averages approximately 5 inches under that of normal children of the same age, indicating dwarfism.

The ability to grow as rapidly as normal children of the same age suggests the presence of a sufficient amount of the growth factor of the anterior lobe of the pituitary gland.

The mental age and the intelligence quotient were not improved by treatment.

E. R. Squibb & Sons furnished the large amount of anterior pituitary extract needed to conduct this experiment, and Mrs. Ray Lending, of the St. Louis Training School for Mentally Defective Children, St. Louis, assisted with the records.

Humboldt Building.

# DIPHTHERIA SCRATCH TEST

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FLUSHING, N. Y.

The scratch test for determining the susceptibility of a person to diphtheria differs from the well known Schick test [1] in that the method is not intracutaneous but cutaneous. The test is therefore performed and read in the same manner as the Pirquet test for tuberculosis,[2] except, of course, that diphtheria toxin instead of tuberculin is used. The work reported here was based on investigations carried out by Reh.[3] So far as my knowledge goes, this test has not yet been introduced in this country.

## ADVANTAGES

The technic is simple and easy to perform and is therefore especially suited to physicians not accustomed to doing routine intracutaneous testing. It does not require syringes and needles. It is less time consuming, particularly when a large number of persons are to be examined. It is less apt to frighten a nervous mother or child. There is little likelihood of producing pseudoreactions, and the results are therefore easy to interpret.

## SUBJECTS

The scratch test was performed routinely on 100 children at the Queens General Hospital, Jamaica, N. Y., and was found to compare favorably with the Schick test. Regardless of the illness for which these patients were admitted to the hospital, there was never any unfavorable reaction to the test. The ages of these children were as follows:

| Age | Cases |
|---|---|
| 3 months | 2 |
| 3-6 months | 2 |
| 6 months to 1 year | 8 |
| 1-2 years | 10 |
| 2-3 years | 13 |

From the Children's Department of the Queens General Hospital, Jamaica, N. Y., City of New York Department of Hospitals, service of Dr. W. C. A. Steffen, director of pediatrics.

1. Schick, B.: Die Diphtherietoxin-Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheilseruminjektion, München. med. Wchnschr. **60**: 2608, 1913.

2. von Pirquet, C.: Tuberculin Diagnose durch kutane Impfung, Berl. klin. Wchnschr. **20**:644 (May 20) 1907.

3. Reh, T.: La cuti-réaction à la toxine diphtérique: Essai de simplification du "Schick" usuel, Schweiz. med. Wchnschr. **64**:513 (June 2) 1934.

| Age | Cases |
|---|---|
| 3-4 years | 6 |
| 4-5 years | 7 |
| 5-6 years | 11 |
| 6-7 years | 11 |
| 7-8 years | 5 |
| 8-9 years | 7 |
| 9-10 years | 8 |
| 10-11 years | 4 |
| 11-12 years | 5 |
| 12-13 years | 1 |
| Total number of cases | 100 |

The material used for testing was a toxin containing 30 flocculating units per cubic centimeter, originally of 1,200 minimum lethal doses per cubic centimeter, prepared by the New York city department of health under the supervision of Dr. Olga R. Povizky. It was kept in a small dark bottle having a medicine dropper attached to the stopper. When not in use it was left in a cool place.

## METHOD

1. The flexor surface of the forearm was cleaned with alcohol or ether.

2. By means of a medicine dropper or a glass rod, a drop of the diphtheria toxin was placed on the upper part of the forearm and another drop 2 to 3 inches (5 to 7.5 cm.) below the first.

3. With a stylet or a border the skin between the two drops was scarified. This was done by twirling the instrument between the thumb and the first finger or by simply scratching the superficial layer of the skin. This was repeated in the areas under the drops of toxin. The material was rubbed into the skin with the end of the glass rod. The middle scratched area, which was not treated with toxin, served as a control. For restless or nervous children it was found more practicable to scarify the skin first and then apply the toxin.

4. The material was allowed to dry. No dressings were used.

5. The borer or stylet and the rod were dipped into alcohol before and after being used.

6. A positive reaction was indicated by the formation forty-eight hours later of a papule 5 to 15 mm. in diameter, definitely palpable as well as visible, with a pustule and crust in the center, surrounded by a circular hyperemic zone with infiltration of surrounding tissues; this reaction reached its height of intensity between the second and the fourth day. The area of scarification which was not treated with diphtheria toxin showed no such reaction and thus served as a control.

On the fourth day the pustule dried up, leaving an area of pigmentation. On the sixth day the infiltration regressed, and the crust disappeared. After eight to fifteen days there were in most cases no visible traces of the former reaction. No scars remained. For comparison, Schick tests were performed simultaneously with the scratch tests, and the results were checked.

## RESULTS

The results as compared with those of the Schick test were as follows: There was complete agreement in 92 per cent of the cases. In 1 case there were a positive Schick reaction and a negative reaction to the

scratch test. However, this patient had been immunized with 1,200 units of antitoxin after the positive Schick reaction, and the scratch test was done several days later. As to the other (7) cases in which there was disagreement, the Schick reaction was negative and the reaction to the scratch test positive in 4 cases and the Schick reaction questionably negative and the reaction to the scratch test positive in 2 cases.

| Cases | Schick Test | Diphtheria Scratch Test |
|---|---|---|
| 55 | Negative | Negative |
| 33 | Positive | Positive |
| 1 | Positive | Negative |
| 4 | Negative | Positive |
| 1 | Negative | Positive (?) |
| 2 | Negative (?) | Positive |
| 4 | Positive (?) | Positive (?) |

Total cases 100

It is thus seen that there was close agreement between the results of the Schick test and those of the scratch test, although the latter seems to be slightly more sensitive. Similar results were obtained by Reh.[3]

## SPECIFICITY OF THE REACTION

That the diphtheria scratch test is specific is well proved by the findings just cited. Furthermore, Novotný and Schick[4] have shown that when diphtheria toxin is mixed with antitoxin there will be no reaction. Moreover, there will be no reaction if twenty-four hours before vaccination with diphtheria toxin an injection of 1,500 to 3,000 units of antitoxin is administered, which immunizes the person against diphtheria. It will be noticed that in 1 case, in which the Schick reaction had been positive, the reaction to the scratch test was negative because the test was made several days after the patient received antitoxin. Again, Novotný and Schick[4] pointed out that the local reaction was more apt to cease if antitoxin was administered intravenously than if it was given subcutaneously. This can be explained by the fact that intravenous administration produces a more rapid and efficient immunization. One must therefore conclude that a positive reaction to the diphtheria scratch test specifically indicates that the patient possesses less than $\frac{1}{30}$ unit of a diphtheria antitoxin in 1 cc. of blood serum. In addition, because of the similar results obtained by the Schick and by the diphtheria scratch test in spite of the enormous differences in the strength of the toxin used, one must assume that in a susceptible person the skin absorbs at least $\frac{1}{50}$ minimum lethal dose of diphtheria toxin to produce a positive reaction to the scratch test.

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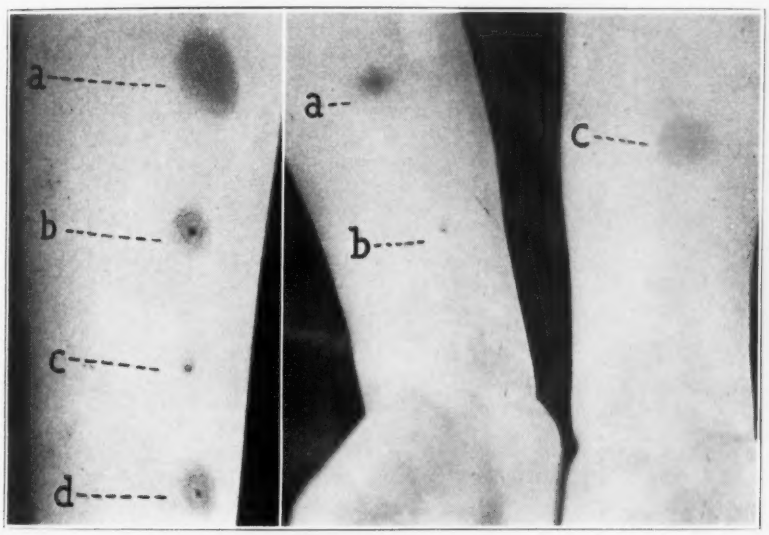
4. Novotný, J., and Schick, B.: Ueber Diphtheriekutanreaktion beim Meerschweinchen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **4**:550, 1910.

### ANALOGY TO TUBERCULIN TESTS

Although the toxins are different, there is an interesting analogy between the cutaneous tuberculin (von Pirquet [2]) test and the diphtheria scratch or cutaneous test. They are performed and read the same way. Both have an incubation period of two to four days, during which antibodies are formed; and one must suppose that with diphtheria toxin as well as with tuberculin some allergic process must be taking place. Tuberculin and diphtheria toxin both act on the skin, and in both tests the skin must absorb a minimum amount of toxin (0.01 mg. of tuberculin and $\frac{1}{50}$ minimum lethal dose of diphtheria toxin, respectively), in order to produce a positive reaction. Both tests are specific




A B

Fig. 1.—Results of diphtheria tests. In *A*, *a* is a positive reaction to the Schick test, *b* a positive reaction to the scratch test, *c* a control and *d* a positive reaction to the scratch test. In *B*, *a* is a positive reaction to the scratch test, *b* a control and *c* a positive reaction to the schick test.

(tuberculin for tuberculosis [5] and diphtheria toxin [4] for diphtheria). When one considers the methods of testing, one may regard the Schick (intracutaneous) test as analogous to the Mantoux test and the diphtheria scratch (cutaneous) test as analogous to the Pirquet test.

Yet diphtheria and tuberculosis are entirely different disease entities. One may have a positive diphtheria and a negative tuberculin reaction, or vice versa. Moreover, only diphtheria antitoxin will modify or suppress the diphtheria reaction, and only tuberculin can influence the

5. Bass, M. M.: Cutaneous and Intracutaneous Tuberculin Tests in Infants and Children, Am. J. Dis. Child. **15**:313 (May) 1918.

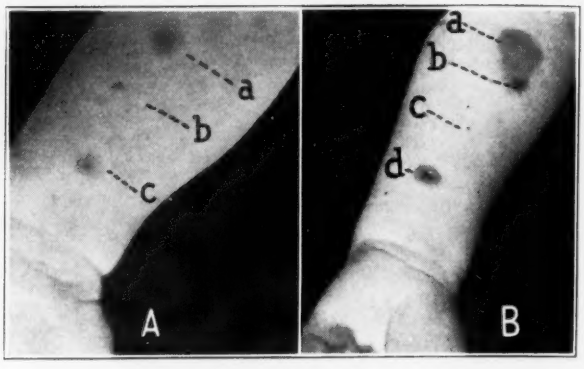



Fig. 2.—*A*, results of the diphtheria scratch test, *a* being a positive reaction, *b* a control and *c* a positive reaction. In *B*, which shows results of diphtheria tests, *a* is a positive reaction to the Schick test, *b* a positive reaction to the scratch test, *c* a control and *d* a positive reaction to the scratch test.

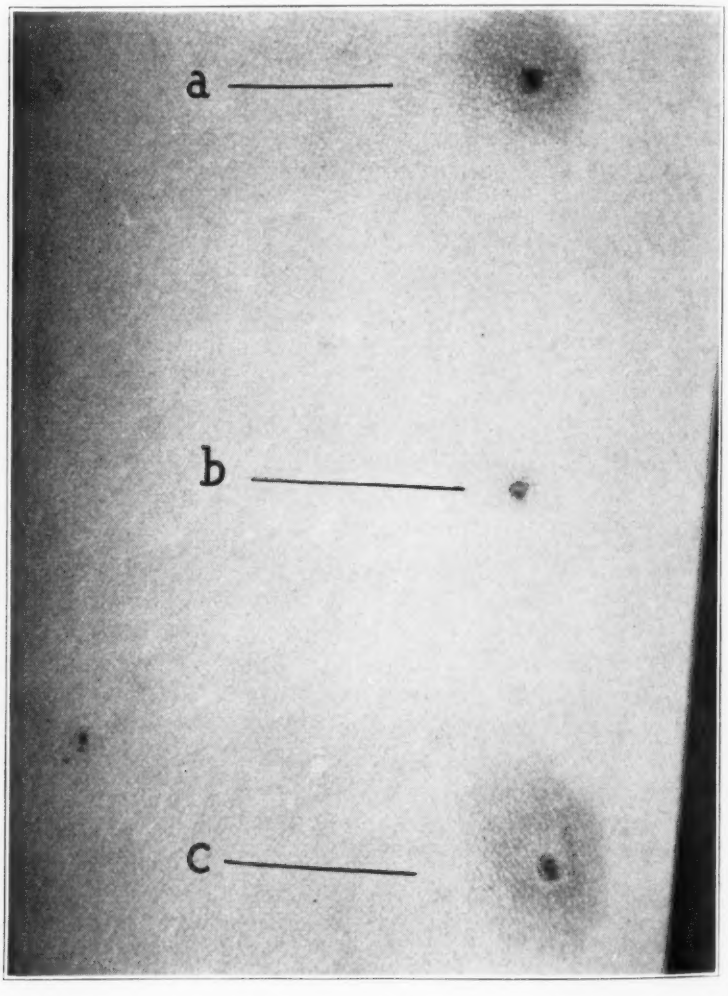



Fig. 3.—Results of the diphtheria scratch test (magnified); *a* is a positive reaction, *b* a control and *c* a positive reaction.

tuberculin reaction. Furthermore, the interpretation of the diphtheria test takes on a different meaning. For it was shown by Wassermann [6] that normally the human organism builds up antitoxic substances, which increase with age, against diphtheria toxin, even if the person was never infected with diphtheria. A negative reaction to the scratch or to the Schick test would therefore indicate that a person possesses sufficient antibodies to render him immune to diphtheria. On the other hand, a positive reaction to the Mantoux, to the Pirquet or to the tuberculin patch test [7] definitely indicates that the person has already been infected with tuberculosis. Hence Pirquet regarded the tuberculin reaction as an apotoxic phenomenon and tuberculosis as an apotoxic disease while considering diphtheria as a primary toxic condition.

Incidentally, one is confronted by the fact that a large number of children (about 40 per cent in this series) are susceptible to diphtheria. A warning of that nature was recently issued by Bundesen,[8] president of the Chicago board of health, who stated that roughly 1 of every 3 children is not protected against diphtheria. If physicians are going to eradicate this disease—and diphtheria is eradicable—testing and immunizing children against it must become universal.

## SUMMARY AND CONCLUSIONS

The diphtheria scratch test is performed and the results read in the same manner as the Pirquet test for tuberculosis.

The material used is a diphtheria toxin of 1,200 minimum lethal doses and of at least 30 flocculating units per cubic centimeter.

The test is specific for diphtheria.

Its results compare favorably with those of the well known Schick test.

Its advantages are that the technic is simple; the test requires no syringes and needles; it is less time consuming, and it is slightly more sensitive.

3619 Bowne Street.

6. Wassermann, A.: Die Immunität Gesunder gegenüber Diphtherietoxin, Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte, 1894, p. 403.

7. Grozin, M.: The Tuberculin Patch Test as a Diagnostic Aid in Tuberculosis, Am. J. Dis. Child. **46**:17 (July) 1933.

8. Disappointments in Diphtheria Prevention, New York State J. Med. **38**:87 (Jan. 15) 1938.

# ANAMNESTIC REACTION OF TUBERCULIN

## PRELIMINARY REPORT

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AND
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By the anamnestic reaction of tuberculin is meant the remembering reaction or, more literally, the reawakening of a dormant tuberculin allergy.

Retesting of groups after varying periods frequently discloses that a small percentage of those who previously reacted positively now react negatively. These persons are said to be in a state of anergy. Their allergy to tuberculin is dormant.

That such variations in tuberculin allergy exist, not only from month to month but from day to day, is commonly accepted. Many factors have been suggested as influencing this fluctuation in sensitivity to tuberculin. Appel and others [1] mentioned the age of the lesion, the stage of the infection (progressive or healing), the introduction of tuberculin as causing increased or decreased sensitivity and possibly induced sensitization. Other authors have pointed out that anergy may be present in an advanced stage of tuberculosis or with other diseases, such as measles or any illnesses which make the patient moribund. Howe [2] suggested that daily variations depend on meteorologic conditions and their relation to peripheral circulation. All of these factors may cause a fluctuation in the allergy to tuberculin.

One of us (J. B. N.) having observed, on occasion, that a second dose of tuberculin, of only moderately increased strength, has caused a severe reaction in a person who reacted negatively to the first dose, suggested that possibly the first dose caused reawakening of dormant allergy. This was then followed by a marked reaction to the second test (strengths used, a 1 : 1,000 and a 1 : 500 dilution of old tuberculin).

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From the Chicago Tuberculosis Institute.

1. Appel, J. M.; Douglas, B. H.; Jocz, T. R., and Willis, H. S.: Relation Between Tuberculin Allergy and Clinical Course, Am. Rev. Tuberc. **36**:303 (Sept.) 1937.

2. Howe, J. S.: Daily Variations in the Tuberculin Reaction: Range of Variation in Tuberculous and Control Subjects, Am. Rev. Tuberc. **37**:264 (March) 1938.

Such a reawakening reaction is frequently seen by allergists in the course of routine cutaneous testing for such conditions as asthma and eczema.

It was with this thought that the work was planned. A group of Negroes, aged 16 to 25 years, were given the tuberculin test; purified protein derivative of one tenth of the second strength was used. The material was prepared on the day of the testing. The left forearm was used. All who reacted negatively in forty-eight hours were retested with purified protein derivative of the same strength. A fresh solution was not prepared, the forty-eight hour old material being used for this second test. This was done in order that any possibility of an error concerning the strength of the material might be avoided. The left forearm was used for the second test also, a distance of at least 4 inches (10 cm.) separating the sites of the two injections. Numerous positive reactors to the second test were noted (table).

That the proximity of the sites of the test cannot be a factor in the positive reactions to the second dose was established by Lincoln, Raia

*Results of Tests Done With Identical Strength of Material*

| First Test | | Second Test | | |
|---|---|---|---|---|
| Number Given | Results | Number Given | Results | Results of All Tests |
| 473 | Pos. 370 (78.22%)<br>Neg. 103 (21.78%) | 103 | Pos. 23 ( 4.86%)<br>Neg. 80 (16.92%) | Pos. 393 (83.08%)<br>Neg. 80 (16.92%) |

and Gilbert.[3] These observers have given repeated injections (four to seven) at intervals of two to five days in the identical site and failed to obtain a positive reaction at any time in a group of 7 children.

Since there was no increase in the strength of the solution for the second test, we must assume that the first test caused the awakening of a dormant tuberculin allergy; otherwise we must suppose an induced sensitivity or a meteorologic upheaval.

Nelson, Mitchell and Brown [4] found that there was little possibility of induced sensitization. They did not explain the irregular pattern of reactions in their work but suggested that injections of tuberculin might cause reawakening of dormant allergy, up to a point, and depress at times, depending on personal factors or weather. In a separate study these same authors [5] found a positive reaction at some time in a group

3. Lincoln, E. M.; Raia, A., and Gilbert, L. A.: Tuberculin Reactions in Children, J. Pediat. **12**:479 (April) 1938.

4. Nelson, W. E.; Mitchell, A. G., and Brown, E. W.: The Possibility of Sensitization to Tuberculin, Am. Rev. Tuberc. **37**:286 (March) 1938.

5. Nelson, W. C.; Mitchell, A. G., and Brown, C. W.: Can Sensitization Be Induced by the Intracutaneous Injection of Tuberculin? J. Pediat. **12**:26 (Jan.) 1938.

who had negative reactions to the first 2 tests. They suggested several possibilities, viz.: a nonspecific reaction, reawakening of the allergy, sensitization or extraneous factors. Many of the persons in this group showed calcifications on roentgen examination, most of which were believed to be tuberculous.

Unfortunately we were unable to do a third test on any of those who reacted negatively to the second test. Much more work must be done along these lines in order that the relative importance of the second test may be determined, especially as to value per se or as to the increase in strength of solution.

# Case Reports

## HISTOPLASMOSIS AND RETICULOENDOTHELIAL HYPERPLASIA

HARRY AGRESS, M.D.
AND
S. H. GRAY, M.D.
ST. LOUIS

In 1905 Darling,[1] while engaged in a search for leishmaniasis in the Panama Canal Zone, encountered a case of obscure splenomegaly in a Martinique Negro. Smears and sections of the organs revealed an organism strongly suggestive of the Leishman-Donovan body. Darling recognized certain morphologic characteristics differentiating this organism from the causative agent of kala-azar, but because of its resemblance he felt that this, too, was a protozoan, and he therefore named it "Histoplasma capsulatum." Subsequently he described 2 other cases.[2] Darling's material was studied in 1912 by da Rocha Lima,[3] who expressed the opinion that these were instances of fungous infection simulating the epizootic lymphangitis of horses due to Cryptococcus farciminosus (Rivolta). Later[4] Darling was said to have concurred in this impression. No other case reports appeared in the literature until 1926, when Watson and Riley[5] uncovered comparable organic changes in postmortem examination of a middle-aged Minnesotan whose death resulted from undiagnosed splenomegaly and terminal pulmonary infec-

From the laboratory of the Jewish Hospital.

This study was aided by the David May–Florence G. May Fund.

1. Darling, S. T.: A Protozoön General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen, and Lymph Nodes, J. A. M. A. **46**:1283 (April 28) 1906.

2. Darling, S. T.: Histoplasmosis: A Fatal Infectious Disease Resembling Kala-Azar Found Among Natives of Tropical America, Arch. Int. Med. **2**:107 (Sept.) 1908; The Morphology of the Parasite and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, J. Exper. Med. **11**:515, 1909.

3. da Rocha Lima, H.: Beitrag zur Kenntnis der Blastomykosen-Lymphangitis Epizootica und Histoplasmosis, Zentralbl. f. Bakt. (Abt. 1) **67**:233, 1912.

4. Meleney, H. E.: The Histopathology of Kala-Azar, in the Hamster, Monkey and Man, Am. J. Path. **1**:147, 1925.

5. Watson, C. J., and Riley, W. A.: A Case of Darling's Histoplasmosis Originating in Minnesota, Arch. Path. **1**:662 (April) 1926. Riley, W. A., and Watson, C. J.: Histoplasmosis of Darling, with Report of a Case Originating in Minnesota, Am. J. Trop. Med. **6**:271, 1926.

tion. In 1931 Crumrine and Kessel [6] reported the fifth case, from California, the striking features of which were marked gastrointestinal involvement and absence of clinical splenomegaly. Knowledge of this disease was considerably enhanced in 1934 by the thorough studies of a group from Vanderbilt University. Dodd and Tompkins [7] observed the parasites in macrophages in the circulating blood of a 6 month old infant at autopsy. The parasite, a fungus, was grown by DeMonbreun [8] from cultures, and its yeast form was found pathogenic for monkeys, in which the human form of the disease was reproduced and from which the organism was recovered. The taxonomy of the fungus was studied by Moore,[9] who placed it among the Coccidioideaceae.

It is the purpose of this report to present another case, that of an infant, in which the diagnosis of histoplasmosis was based on autopsy material, and to describe an unusual type of hyperplasia of the reticuloendothelial tissue.

## REPORT OF A CASE

B. R., a boy aged 7 months, was admitted to the Jewish Hospital on Dec. 22, 1936, because of recurrent epistaxis which began one month previously. The parents stated that the patient perspired profusely at night, failed to gain weight and had some slowly healing sores about his lips. The mother had had pulmonary tuberculosis, for which she had been institutionalized ten years previously and which had been arrested. The family history was otherwise irrelevant.

On admission the infant appeared malnourished and underdeveloped. His temperature was 102 F. The skin was pallid; no petechiae or eruptions were present. The nose was of the saddle type, with perforation of the cartilaginous portion of the nasal septum and mucopurulent rhinitis. Lesions about the mouth were suggestive of rhagades. A small ulcer appeared in the buccal mucosa. There was no cervical lymphadenopathy. The chest showed slight changes in the percussion note and breath sounds posteriorly. The edge of the liver was palpated 2 fingerbreadths below the costal margin, and the spleen was markedly enlarged. There were a few fissures about the anus. Bowing of the tibias suggested rickets.

Because of the nasal lesion and the sores about the mouth, even though results of the serologic examination were negative, a diagnosis of congenital syphilis was made, and the child was given one parenteral injection of an antisyphilitic drug. Other therapy was symptomatic. The patient's course in the hospital was progressively downhill, with temperatures ranging between 98 and 102.4 F. Marked

6. Crumrine, R. M., and Kessel, J. F.: Histoplasmosis (Darling) Without Splenomegaly, Am. J. Trop. Med. **11**:435, 1931.

7. Dodd, K., and Tompkins, E. H.: A Case of Histoplasmosis of Darling in an Infant, Am. J. Trop. Med. **14**:127, 1934.

8. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's Histoplasma Capsulatum, Am. J. Trop. Med. **14**:93, 1934.

9. Moore, M.: (*a*) Posadasia Pyriformis and Posadasia Capsulata, Two Causative Organisms of Darling's Histoplasmosis in the United States, Ann. Missouri Botan. Garden **21**:347, 1934; (*b*) A Morphological and Physiological Study of Two Species of Posadasia: P. Capsulata (Darling) Moore and P. Pyriformis Moore, ibid. **22**:335, 1935.

pallor developed. The spleen and liver increased in size. The patient died nineteen days after admission (or approximately seven weeks after the onset of symptoms) with what clinically appeared to be bronchopneumonia.

*Laboratory Examinations.*—The urine was normal. The Kahn and Wassermann reactions of the blood and the spinal fluid were negative. The Kahn reaction of the blood of both parents was negative. Cultures of blood and spinal fluid were negative. Cultures of material from the nose and throat were negative for diphtheria bacilli. The results of blood counts were as follows:

| Date | Red Blood Cells | Hemoglobin, % | White Blood Cells | Basophils, % | Eosinophils, % | Myelocytes, % | Juvenile Cells, % | Staff Cells, % | Segmented Cells, % | Lymphocytes, % | Monocytes, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12/28/36 | 4,430,000 | 72 | 6,700 | 0 | 1 | 0 | 0 | 3 | 62 | 29 | 5 |
| 1/ 4/37 | 3,140,000 | 66 | 5,850 | 0 | 0 | 0 | 0 | 4 | 47 | 42 | 7 |
| 1/ 5/37 | ..... | .. | ..... | 1 | 0 | 0 | 2 | 7 | 31 | 55 | 4 |

The blood smears showed slight evidence of a regenerative type of anemia. There was no evident thrombopenia. Roentgen study of the legs showed no evidence of pathologic change of the bone. Roentgen examination of the chest revealed increased pulmonary fibrosis suggesting diffuse bronchitis.

*Clinical Diagnoses.*—These were (*a*) congenital syphilis; (*b*) obscure malignant changes; (*c*) undetermined blood dyscrasia; (*d*) bronchopneumonia; (*e*) sepsis, and (*f*) rickets.

*Postmortem Examination.*—Gross Study: The body was poorly nourished and poorly developed. The skin was pale. There was no lymphadenopathy. The posterior fontanel was closed; the anterior fontanel was partially open. The scleras and mucous membranes were pale. There was a small irregular perforation of the cartilaginous portion of the nasal septum. On the inner surface of the lower lip in the midline was a small ulcer which had healed somewhat by the formation of scar tissue and had dimpled the lip. There was a small herniation at the umbilicus. Several minute fissures surrounded the anus. The tibias were bowed. The subcutaneous fat was scant. The peritoneal cavity contained a small amount of clear fluid. The organs were normally disposed. The peritoneum was everywhere pale, smooth and glistening. The liver extended 3 cm. below the costal arch in the midclavicular line. The thorax contained no free fluid. There were no adhesions between the lungs and the wall of the chest. The pericardial sac contained no fluid. The pericardium was smooth, pale and glistening throughout.

The endocardium was everywhere pale, smooth and delicate. The myocardium was beefy red and firm. In places there were minute yellowish areas.

The lungs were grayish and somewhat firm. On section, irregular consolidated grayish areas separated the honeycombing of alveoli. The interlobular demarcations were prominent. The vessels and bronchi could easily be followed to their smallest ramifications because of their increased linear grayness.

The spleen was approximately twice the normal size. It cut with some increased resistance. The pulp had a reddish slate color and was firm. An accessory spleen approximately 0.5 cm. in diameter was situated near the tail of the pancreas.

The liver was somewhat increased in size and was brownish red. It cut with no increased resistance.

The gallbladder appeared normal.

The pancreas was of normal size and disposition. There was no increased firmness. Around the pancreas many small lymph nodes were lodged in the mesentery; on section these appeared whitish.

Through the entire large bowel were many tiny fresh superficial ulcerations.

Both kidneys were of normal size. Their markings were distinct.

The ureters, bladder and prostate showed no changes worthy of note.

The adrenals appeared normal.

Histologic Study: The predominant feature of the lungs was the obliteration of architecture by aggregations of mononuclear cells of varying morphologic characteristics (fig. 1). Polymorphonuclear leukocytes were entirely absent, but there were a few plasma cells, lymphocytes and giant cells of the Langhans type. Of the mononuclear cells, the most interesting varied from 12 to 20 microns in diameter and were oval or polygonal. The nuclei were ovoid or tended to lobulate, had relatively sparse chromatin and a fairly thick, well defined membrane and contained one or two irregularly shaped nucleoli. The cytoplasm was granular or foamy and stained faintly pink in the sections prepared with hematoxylin and eosin. A striking feature was their phagocytosis of small ovoid or circular bodies 2 to 4 microns in diameter, which were identified as parasites.[10] These bodies appeared to be within vacuoles in the cytoplasm, and each was delimited by a fine membrane within which was a very small, irregularly staining mass of variable shape, generally in an excentric position. The space between the outer limiting membrane

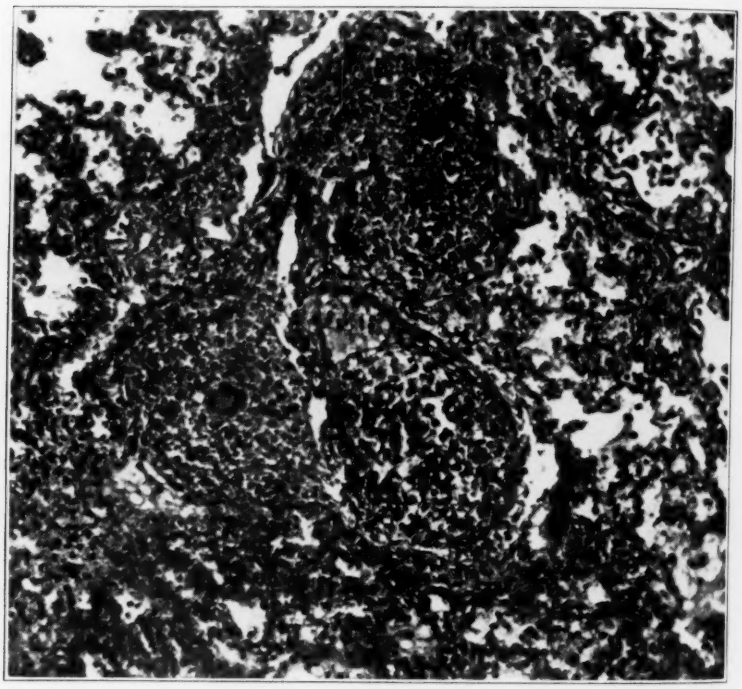

Fig. 1.—Section of lung showing marked accumulation of monocytic cellular infiltrate. Note the two giant cells of the Langhans type and the capillary almost completely filled with phagocytic cells. Magnification, × 100.

10. Identified by Dr. Hal Downey (University of Minnesota). Dr. Morris Moore (Barnard Skin and Cancer Hospital, St. Louis) confirmed the diagnosis.

and the stained mass of the parasites was achromatic. Individual phagocytic cells contained 2 to 10 or more parasites, which occasionally were so numerous as to displace the nucleus. Some of the parasites were extracellular as well as intracellular. The so-called dust cells of the lung contained phagocytosed bodies as well as particles of carbon.

An unusual and interesting feature of the reaction in the lungs was the formation of tumor-like projections into the lumens of arterioles (fig. 2). The entire wall of a vessel where this process had taken place was intact, as judged by serial sections and special stains. In all sections a single layer of endothelium of fairly

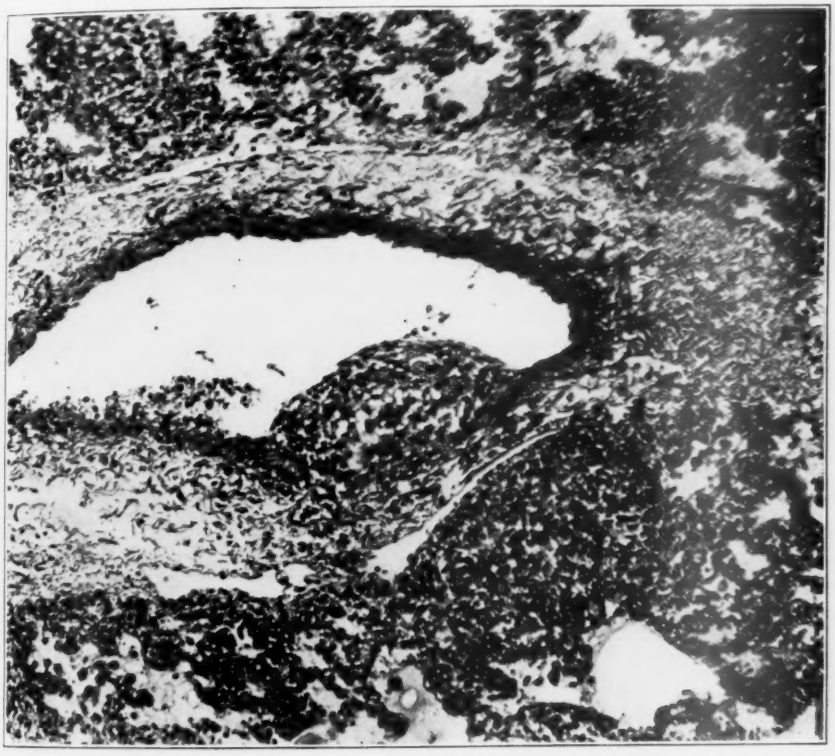

Fig. 2.—Medium-sized vessel of the lungs, showing the subendothelial tumor. Magnification, × 100.

normal appearance covered the lesions. The endothelial cells were morphologically different from the cells forming the main portion of the blood vessel tumors (fig. 3), which in turn corresponded to the phagocytic cells in the pulmonary parenchyma. Most of the capillaries (fig. 1) were occluded by accumulations of phagocytic cells, which appeared to be embolic masses within the vessels rather than formations of local origin, such as those seen in the larger vessels.

The degree of change in different mesenteric lymph nodes was roughly proportional to the numbers of invading parasites. In some areas necrotic masses of pink-staining granular material had replaced the normal lymphoid tissue (fig. 4). It was especially in and around these areas of necrosis that there were numerous

Fig. 3.—Oil immersion view of the tumor seen in figure 2, showing the endothelial lining covering the tumor and its continuity with the lining of the rest of the vessel. Note the parasites in the phagocytic cells in the upper left corner. Magnification, × 1,000.

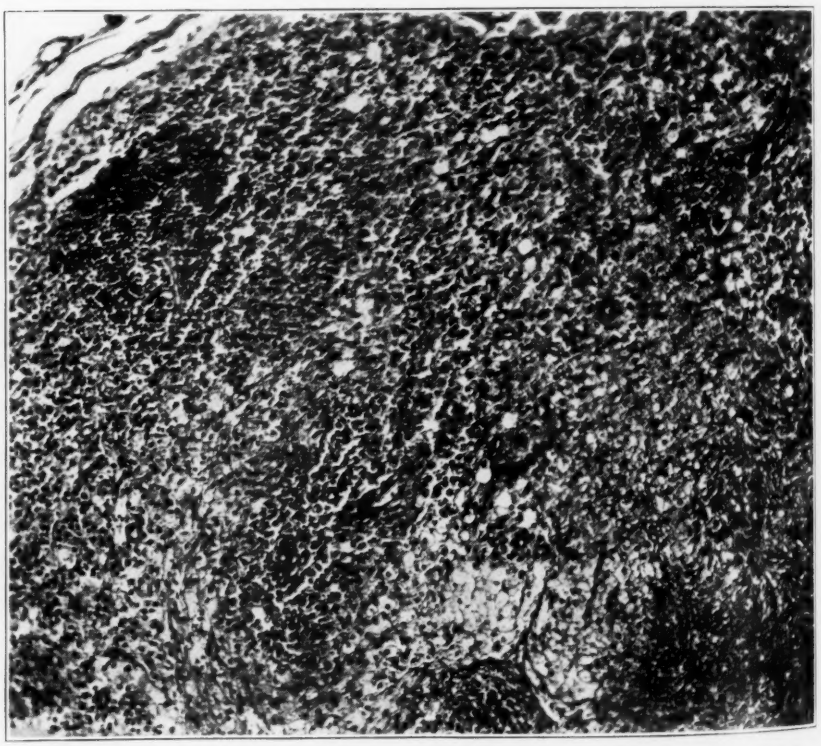

Fig. 4.—Lymph node, showing marked destruction of architecture. The remains of a lymph follicle can still be discerned. Magnification, × 60.

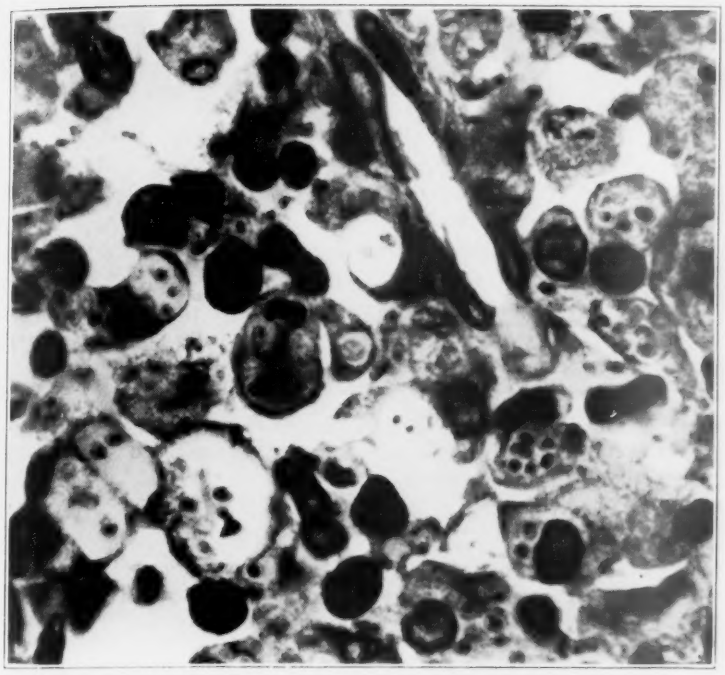

Fig. 5.—Oil immersion view of the section seen in figure 4, showing numerous parasites within phagocytic cells. An occasional extracellular parasite is present. Note the mitotic figure in telephase. Magnification, × 1,000.

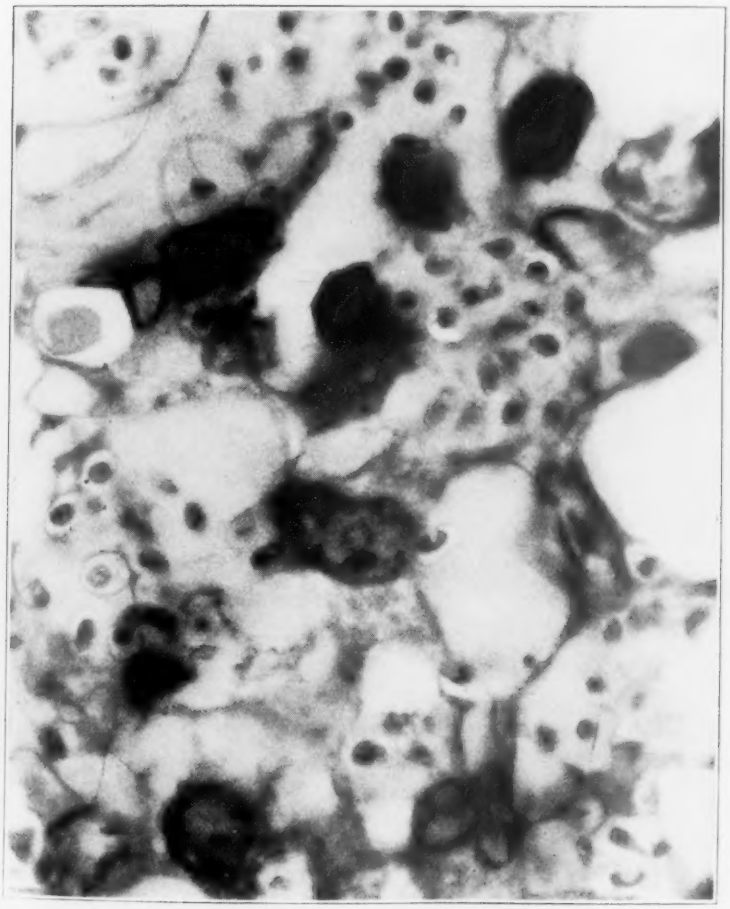

Fig. 6.—Oil immersion view, showing numerous parasites. Note the nonstaining capsule around the organism. Magnification, × 2,000.

phagocytic cells similar to those seen in the lungs. Morphologic alterations in these cells were much more striking than in those of the pulmonary tissue; at times there remained nothing more than the outline of a cell glutted with parasites (figs. 5 and 6). Rarely a mitotic figure was observed in the mononuclear phagocytic cells. Surrounding the areas of necrosis were plasma cells which were occasionally phagocytic. In the lymph nodes in which massive destruction of the architecture had not occurred, phagocytosis of parasites by littoral and general reticulum could be observed. Here the sinuses were distended and contained parasites in both the intracellular and the extracellular phase. Although the phagocytic process in the lymph nodes was concerned chiefly with parasites, occasional cells contained remnants of lymphocytes ("tingible bodies") and red blood cells, both of which could be readily differentiated from the parasites.

In the liver there were slight and irregularly distributed necrosis and infiltration of phagocytic cells, chiefly periportal. The cellular elements were similar to those previously described. Some parasites were free in the sinuses and some were in Kupffer cells. Many of the central veins were full of phagocytic cells. Rare giant cells of the Langhans type were present. There was only a slight increase in connective tissue.

The spleen was markedly congested, and the malpighian corpuscles were slightly less conspicuous than normal. Phagocytic cells similar to those in other organs were fairly numerous; they contained ingested particles of blood pigment as well as parasites. The phagocytosis occurred chiefly in the cells of the parenchyma of the spleen, but the cells of the littoral reticulum were engaged in the process as well. The accessory spleen presented a picture similar to that of its parent organ.

In some areas of the colon enlarged follicles covered by normal mucous membrane were to be seen, whereas in other regions ulceration extended down to the follicles. The follicles consisted chiefly of lymphocytes, but occasionally phagocytic cells containing parasites were seen here.

In the heart small areas of invasion by phagocytic cells, chiefly perivascular in distribution, had destroyed the muscle fibers. The cells were similar to those already described.

In the nasal septum, between the mucous membrane and the cartilage, a rare parasite was observed.

The final diagnosis was histoplasmosis involving the lungs, lymph nodes, spleen, liver, gastrointestinal tract, heart muscle and nasal septum.

## COMMENT

From a survey of the symptoms in the accepted cases reported in the literature (table 1) it is readily apparent that the diagnostic possibilities are numerous, a fact which is evident from the clinical diagnoses suggested by the various authors. Darling presented chronicity, fever, emaciation, anemia, leukopenia and splenomegaly as the cardinal symptoms and signs of the disease, not all of which have been regularly mentioned in subsequent case reports. The duration of the disease has varied from three weeks to eight months, although in 1 case the patient was known to have had splenomegaly for eight years. In this instance,

TABLE 1.—*Summary of Clinical Observations*

| Author | Darling (case 1) | Darling (case 2) | Darling (Case 3) | Watson and Riley | Crumrine and Kessel | Dodd and Tompkins | Agress and Gray |
|---|---|---|---|---|---|---|---|
| Date of publication | 1905 | 1909 | 1909 | 1926 | 1931 | 1934 | 1937 |
| Origin | Panama Canal Zone | Panama Canal Zone | Panama Canal Zone | Minnesota | California | Tennessee | Missouri |
| Age, sex | 27 yr., male | 29 yr., male | 55 yr., male | 52 yr., female | 42 yr., male | 6 mo., male | 7 mo., male |
| Race | Martinique Negro | Martinique Negro | Chinese | White | Mulatto | White | White |
| Lungs | Normal | Signs of pneumonia | ..... | Bronchopneumonia; hemoptysis | Cough and rales; roentgen study showed marked fibrosis | Cough; roentgen study showed marked infiltration suggesting severe bronchitis | Roentgen study showed increased pulmonary fibrosis; bronchopneumonia |
| Liver | ..... | Extended 2 finger-breadths below costal margin | ..... | Large and hard | ..... | Enlarged and firm | Extended 2 finger-breadths below costal margin |
| Spleen | Enlarged | Palpable | ..... | Large and hard | No enlargement | Extended to umbilicus | Markedly enlarged |
| Gastrointestinal tract | Vomiting | Vomiting and diarrhea | ..... | Ascites | Severe diarrhea; palpable mass in abdomen | Vomiting | Fissures about anus |
| Temperature | 95-101 F. | Irregular fever | 97.5-102 F. | 99-101 F. | 99-102.5 F. | 100 F. | 98-102.4 F. |
| Pulse rate | 96-120 | ..... | 98-120 | ..... | 90-120 | 140 | Tachycardia |
| Other findings | Emaciation | Emaciation | Coma; emaciation | ..... | Weakness and anorexia | Jaundice and edema | Nasal perforation; rhagades |
| Duration | 11 weeks | More than 3 weeks | Approximately 5 months | Terminal course 4 weeks | 8 months | 5 weeks | 7 weeks |
| Red blood cells | ..... | ..... | ..... | 3,830,000 | 3,120,000; 2,900,000 | 2,070,000 | 3,140,000; 4,430,000 |
| White blood cells | 2,200 | ..... | ..... | 3,000-4,600 | 3,600-4,500 | 11,640-17,700 | 5,850-6,750 |
| Hemoglobin | 60 per cent | ..... | ..... | 85 per cent | 70 per cent | 6.4 Gm. | 66-72 per cent |
| Differential count, % | ..... ..... | ..... | ..... | Polymorphonuclears 67; monocytes 12 | Polymorphonuclears 80-86 | Monocytes 12.5 | Lymphocytes 29-55; monocytes 4-7 |
| Stools | Normal | ..... | ..... | ..... | Numerous yeasts | ..... | ..... |
| Urine | ..... | ..... | ..... | Moderate amount of albumin; occasional casts | Albumin trace; sugar 0.3 per cent | Albumin and casts | Normal |
| Wassermann or Kahn reaction | ..... | ..... | ..... | ..... | Blood and spinal fluid, negative | ..... | Blood and spinal fluid, negative |
| Cultures and other laboratory examinations | Smears of organs showed organisms; named Histoplasma capsulatum | Parasites in smears of organs | Parasites in smears of organs | Sputum contained no tubercle bacilli | Sputum contained no tubercle bacilli | Fungus cultured from blood and organs | Blood negative |
| Clinical impressions | ..... | ..... | ..... | Banti's disease; Gaucher's disease | Obscure malignant growth; tuberculous peritonitis | Primary blood dyscrasia; parasites noted antemortem in circulating blood | Rickets; blood dyscrasia; congenital syphilis; malignant growth; sepsis; terminal bronchopneumonia |

however, the terminal picture was that of a subacute disease lasting four weeks. Leukopenia was present in all cases but 1. The association of leukopenic states with splenomegalic disease is so common that this finding is of no great significance in the differential diagnosis. Splenomegaly was prominent in all cases with 1 exception, in which the spleen was not palpated but at autopsy was observed to be of twice the normal size. In addition to the criteria elaborated by Darling, hepatic, pulmonary and gastrointestinal signs and symptoms have been prevalent. The degree of hepatomegaly varied, but in 4 cases there was obvious clinical enlargement. In all instances in which examinations were recorded, some degree of pulmonary involvement was revealed by either roentgen or physical examination. In 1 case hemoptysis featured the pulmonary complaint. In 4 cases participation of the gastrointestinal tract in the disease process was clinically evident, and in 1 case this aspect was so prominent that a diagnosis of tuberculous peritonitis was conjectured.

From the standpoint of the laboratory the diagnosis was established ante mortem but once; in that instance the parasites were found in monocytic cells in a sample of circulating blood taken two days before death. Crumrine and Kessel noted numerous yeasts in the stool cultures in their case but failed to recognize their significance. The possibility suggests itself that the organisms may be observed on direct examination or culture of the stools. In the present case direct smears of the nasal discharge might have revealed the parasites, since they were seen in the sections of the nasal septum. When splenic puncture or biopsy is resorted to as a diagnostic procedure, search of the material for this fungus should be made. It is even conceivable that the organism may be visible on direct examination or culture of the sputum in cases in which pulmonary involvement occurs.

The descriptions of the parasite have been consistently similar; they correspond to the bodies frequently mentioned in the histologic description of the organs in the present case report. Darling thought that he saw flagellated forms in smears of his material, but da Rocha Lima considered these to be artefacts. Crumrine and Kessel described large forms in the spleen as an extracellular phase of the fungus. DeMonbreun established the pathogenicity of the yeastlike form in animals. Neither the mycelial nor the yeastlike forms of the fungus have been observed occurring free in nature. The taxonomy of the parasites recovered in the 2 cases mentioned was studied by Moore, who placed them in the family Coccidioideaceae. In the genus Posadasia he differentiated two species, capsulatum and pyriformis. The former is the organism involved in Dodd and Tompkins' case of histoplasmosis, whereas the

latter is the fungus grown from the lesions in Hansmann and Schenken's [11] case of chronic dermatitis. In sections the organisms are apparently identical, and it is only on the basis of cultural characteristics that the two species can be differentiated.

The organic changes, which are summarized in tables 2 and 3, involved the reticuloendothelial system. It is generally conceded that embryonic mesenchyme possesses the capacity of differentiating into blood cell elements, histiocytes (phagocytic cells), vascular endothelium and fibroblasts (connective tissue cells). Whether there is retention of this multipotentiality by certain widespread tissues of the adult organism, and whether these more or less differentiated elements can revert to other types, are decidedly moot questions. Whatever histogenetic relation may exist between the loose connective tissue, the reticulum of the spleen and lymph nodes, the Kupffer cells of the liver and the vascular endothelium, their affinity for colloidal dyes under certain conditions has been invoked as a basis of functional similarity (if not identity) under the general term "reticuloendothelial system," suggested by Aschoff and Kiyono.[12] Since the experimental observations of these workers, a voluminous literature concerning disturbances of this system has accumulated in the clinical as well as the experimental field. The various writers on the subject have most prominently concerned themselves with two major aspects of the problem, namely, the classification of disease processes and the derivation of cellular elements.

It is not our intention to attempt anything approaching an exhaustive discussion of the problems of classification, for the inadequacy of a critique short of monographic proportions is obvious. No useful pur-

11. Although the cases reviewed in the tables are classical examples of histoplasmosis, other questionable or atypical cases have been reported. C. J. Watson (The Pathology of Histoplasmosis [Darling] with Special Reference to the Origin of the Phagocytic Cells, Folia haemat. **37**:70, 1928) briefly referred to Wade's case, in which the involvement was primarily pulmonary. The case reported by Phelps and Mallory (cited by Dodd and Tompkins [7]) was seriously questioned by DeMonbreun.[8] G. H. Hansmann and J. R. Schenken (A Unique Infection in Man Caused by a New Yeast-Like Organism, a Pathogenic Member of the Genus Sepedonium, Am. J. Path. **10**:731, 1934) described involvement in a middle-aged man in which chronic generalized dermatitis and lymphadenopathy were the predominant features. Moore [9b] placed the causative fungus of this case in close relation to the organism involved in the cases considered in the present report.

12. (*a*) Aschoff, L., and Kiyono, K.: Zur Frage der grossen Mononukleären, Folia haemat. **6**:213, 1913. (*b*) Aschoff, L.: The Reticulo-Endothelial System, in Lectures on Pathology, New York, Paul B. Hoeber, 1924.

TABLE 2.—*Summary of Gross Pathologic Observations*

| Author | Darling (case 1) | Darling (case 2) | Darling (case 3) | Watson and Riley | Crumrine and Kessel | Dodd and Tompkins | Agress and Gray |
|---|---|---|---|---|---|---|---|
| Lungs | Subpleural and parenchymal hyaline miliary nodules | Bronchopneumonia; no granulomas | Large hyaline granulomas surrounded by areas of hemorrhage | Bilateral pleural effusion; patchy consolidation suggesting unresolved bronchopneumonia | Basal involvement apparently bronchopneumonia | Mottled appearance; organs larger and heavier than normal | Firm, dark gray areas involving most of both lungs |
| Gastrointestinal tract | Small superficial ulcers in cecum and ileum | ..... | Severe ulceration of jejunum, ileum and colon | Ascites | Severe ulcerative colitis | ..... | Small amount of ascites; superficial ulceration of colon |
| Liver | Enlarged and pale; slight atrophic cirrhosis | No macroscopic necrosis | Extensive periportal necrosis and cirrhosis | Extended 10 cm. below costal margin; "hobnail" cirrhosis | Accentuation of normal lobulation | Greatly enlarged; generalized central necrosis | Increased size; cut surface normal |
| Spleen | Enlarged to three times normal size; pulp firm; small yellow nodules resembling tubercles | Markedly enlarged | Markedly enlarged; malpighian bodies indistinct | Weight 1,450 Gm.; firm and hemorrhagic; two accessory spleens | Weight 210 Gm.; white nodules suggesting Hodgkin's disease | Greatly enlarged | Twice normal size and firm |
| Lymph nodes | Mesenteric nodes and those at hilus of spleen enlarged; peribronchial nodes caseous | Changes as in case 1 | Changes as in case 1; postperitoneal nodes greatly enlarged | Peritoneal nodes enlarged, discrete and pale red | Tremendous mass of nodes in mesentery; many caseous | ..... | Enlarged nodes in region of pancreas |
| Other organs | Heart and muscles atrophic; pia-arachnoid edematous and adherent to brain | Heart and muscles atrophic | Heart and muscles atrophic; skin showed a few recent papules | ..... | Heart had gelatinous coating suggesting tuberculosis | ..... | Perforation of nasal septum |
| Provisional anatomic diagnosis | Acute miliary tuberculosis; tuberculous adenitis; chronic splenitis; atrophic cirrhosis; chronic leptomeningitis; ulcerative enterocolitis | ..... | ..... | Cirrhosis of liver; splenomegaly; lymphadenopathy; unresolved bronchopneumonia; healed tuberculosis; ascites; hydrothorax; nephrosis | ..... | ..... | Unresolved bronchopneumonia; splenomegaly; hepatomegaly; ulcerative colitis; perforation of nasal septum |

TABLE 3.—*Summary of Microscopic Observations*

TABLE 3.—*Summary of Microscopic Observations*

| Author | Darling (case 1) | Darling (case 2) | Darling (case 3) | Watson and Riley | Crumrine and Kessel | Dodd and Tompkins | Agress and Gray |
|---|---|---|---|---|---|---|---|
| Lungs | Alveolar walls desquamating; cells containing many parasites; cytoplasm of infected cells almost gone; parasites rarely free; polymorphonuclears rare | Picture of bronchopneumonia; no parasites seen | Observations as in case 1 | "Mononuclear type of pneumonia;" "septal cells" phagocytic; some hyalinization | Scattered phagocytic cells packed with organisms | Areas of necrosis and massive infiltration by large phagocytic mononuclear cells | Invasion by free and phagocytized parasites; formation of endothelial tumor by phagocytic cells |
| Gastrointestinal tract | ..... | ..... | Ulcer in ileum; mass of cells containing parasites | ..... | Ulcers, with parasites in cells of mucosa and phagocytic cells in submucosa | ..... | Ulceration of mucosa; enlarged lymphoid follicles with occasional parasites |
| Liver | Areas of necrosis with myriads of parasites; areas in which liver cells and endothelial cells were transformed by invading parasites | Small necrotic areas with numerous parasites within cells; "earliest lesion is invasion of endothelial cells" | Tremendous destruction with partial replacement by connective tissue; many parasites free and in cells | Chronic periportal proliferative and exudative lesions; phagocytosis by Kupffer cells | Periportal areas containing phagocytic cells | Central destruction of lobules; sinusoids packed with free phagocytic cells; Kupffer cells actively phagocytic | Slight periportal infiltration; Kupffer cells slightly phagocytic; central veins infiltrated |
| Spleen | Engorgement; increase in connective tissue; numerous free parasites and some in cells | Hemorrhagic; slight atrophy of malpighian corpuscles; scattered monocytic cells engorged with parasites | Hemorrhagic; marked atrophy of malpighian corpuscles with increase in fibrous tissue; littoral reticulum phagocytic | Congestion and fibrosis; hyaline degeneration of reticulum; many giant cells | Parasite noted in extracellular as well as intracellular phase | Tremendous infiltration of both sinusoids and tissue spaces by monocytic cells | Hemorrhagic; veins distended with phagocytic cells; accessory spleen showed alterations similar to those in parent organ |
| Lymph nodes | Cloudy swelling and necrosis; numerous parasites amid débris | Diffuse hyperplasia of lymphoid elements with a few cells containing parasites | Fibrous replacement of normal elements | Hyaline degeneration of reticulum striking; many parasites and giant cells | Caseous necrosis of central portions; numerous phagocytic cells in periphery | Changes as in spleen; mitotic figures frequent in cells lining sinusoids | Reticular hyperplasia or necrosis; large cells containing parasites; occasional mitotic figur |
| Other organs | ..... | ..... | ..... | Adrenals necrotic with invasion by parasites | ..... | Invasion of brain, skin and bone marrow | Invasion of heart muscle and nasal septum |
| Comment | ..... | ..... | ..... | Hyaline changes prominent | Extracellular phase of organism in spleen | ..... | Involvement of endothelium of blood vessels in lung |

pose would be served by such endeavor, since reviews[13] have been adequate. That there have been differences of opinion deserves comment. A number of factors have contributed to what at times appears to be utter confusion, with its resultant discouragement, especially to the clinician. Not the least of these factors consists of the labyrinthine endeavors in hair-splitting nosology, comparable to the dialecticism of theologians. One is inclined to paraphrase Cowdry[14] in decrying that the battle of nomenclature has left tombstones of reputation rather than milestones of achievement. The fact that the problem has been studied by observers with varied interests, that is, by clinicians, pathologists, histologists and hematologists, has abetted this divergence of opinion, especially because of the stress that each group has given minute differences between various aspects of the disease processes. There have been, however, a growing consciousness of the artificiality of limited categorization and a greater appreciation of the interrelation of the various diseases concerned, an attitude succinctly presented by Waugh,[13f] who urged that the similarities be stressed rather than that the differences be contested. With this broad point of view there appears to be some hope of reconciliation of the diverse schemata suggested. The definitive positions of certain diseases can be retained, if for no other purpose than to meet the needs of utility and the necessity for a certain amount of didacticism. At the same time, a channel is left open for the approach to some of the more poorly defined diseases.

Among the disorders of the reticuloendothelial system that more or less defy classification, there has been reported a group of somewhat similar states under a great variety of titles, such as reticuloendotheliosis, infective reticuloendotheliosis, acute infective histiocytosis and, most recently, Letterer-Siwe's disease. The last-mentioned designation was suggested by Abt and Denenholz[15] for 9 reported cases of idiopathic

13. (*a*) Aschoff.[12b] (*b*) Bloom, W.: The Origin and Nature of the Monocyte, Folia haemat. **37**:1, 1928. (*c*) Maximow, A.: Bindgewebe und blutbildende Gewebe, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie, Berlin, Julius Springer, 1924, vol. 2. (*d*) Klemperer, P.: The Relationship of the Reticulum to Diseases of the Hematopoietic System, in Contributions to the Medical Science in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 2, p. 655. (*e*) Hittmair, A.: Zur Frage der sogenannten Retikuloendotheliosen, Folia haemat. **37**:321, 1928. (*f*) Waugh, T. R.: The Interrelation of Various Systemic Hematopoietic Processes, Am. J. M. Sc. **193**:337, 1937.

14. Cowdry, E. V.: A Textbook of Histology, Philadelphia, Lea & Febiger, 1934, p. 30.

15. Abt, A. F., and Denenholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia of Nonlipoid-Storing Macrophages; Discussion of the So-Called Reticulo-Endothelioses, Am. J. Dis. Child. **51**:499 (March) 1936.

progressive splenohepatomegaly occurring in infants. The syndrome is featured by a hemorrhagic diathesis, generalized lymphadenopathy and occasionally the formation of tumors of the bone. The examination of the peripheral blood reveals no distinctive features other than nonregenerative anemia and occasionally leukopenia. The histologic picture is characterized by widespread hyperplasia of macrophages in which a "definite increase in reticular fibers can be demonstrated." Before passing any judgment on the necessity or utility of pigeonholing this group of cases under a new name, we wish to state that we were impressed by the fact that this syndrome is similar to that occurring both in infants and in adults in other cases reported in the literature.[16] The problem of just where to draw the line of demarcation is extremely difficult, a fact which can be readily appreciated if comments are limited to the small group of cases considered by Abt and Denenholz.

It appears that the sine qua non of acceptance in this group has been the establishment of (or rather, the failure in establishing) the cause of the condition. Most prominently mentioned has been the question of the presence or absence of infection, but a review of the original reports of cases brings forth a series of intriguing contentions. Letterer,[17] who reported the original case of the Abt-Denenholz series, expressed the opinion that infection in his case was coincidental, an assumption that the latter authors accepted in developing their group of cases. However, Akiba's case[18] was included in the series despite that author's statement that "there appears to be no doubt that the cell increase is primarily influenced by a septic infection and not a previously existing change" and that he saw "no reason why this disease should be given a separate name, such as aleukemic reticulosis." Foot and Olcott,[19] whose case was accepted by Abt and Denenholz, considered a toxic or infectious factor as the cause, because Staphylococcus aureus haemolyticus was cultured from the blood stream. The infant reported by Guizetti[20] had bilateral otitis media, and streptococci were observed in the spleen post

16. Goldzieher, M., and Hornick, O. S.: Reticulosis, Arch. Path. **12**:773 (Nov.) 1931. Tschistowitsch, T., and Bykowa, O.: Retikulose als eine Systemerkrankung der blutbildenden Organe, Virchows Arch. f. path. Anat. **267**:91, 1928.

17. Letterer, E.: Aleukämische Retikulose (Ein Beitrag zu den proliferativen Erkrankungen des Reticuloendothelial-Apparates), Frankfurt. Ztschr. f. Path. **30**: 377, 1924.

18. Akiba, R.: Ueber Wucherung der Retikulo-Endothelien in Milz- und Lymphknoten und ihre Beziehung zu den leukämischen Erkrankungen, Virchows Arch. f. path. Anat. **260**:262, 1926.

19. Foot, N. C., and Olcott, C. T.: Report of a Case of Non-Lipoid Histiocytosis (Reticuloendotheliosis) with Autopsy, Am. J. Path. **10**:81, 1934.

20. Guizetti, H. U.: Zur Frage der infektiös bedingten Systemkrankungen des reticuloendothelialen Apparates in Kindesalter, Virchows Arch. f. path. Anat. **282**:194, 1931.

mortem. Guizetti would include the case of Schultz, Wermbter and Puhl [21] among this group, although Siwe [22] and Abt and Denenholz would exclude it on the basis that infection was obviously present. The latter authors excluded the case of Van Creveld and Ter Poorten [23] on the same grounds. Gittins [24] suggested that the hyperplastic changes in the reticuloendothelial system in his case comprised the mode of termination of "erythronoclastic" anemia rather than infection. It is our opinion that in the present case the condition conformed with many of the criteria established for Letterer-Siwe's disease and that this diagnosis would be acceptable were it not for the fact that the cause was identified. It is conceivable that in some of these cases further study might have revealed the presence of parasites.

Whatever the cause of the process, the one feature common to all these cases was widespread hyperplasia of the reticuloendothelial system; they might be grouped under the term "reticuloendotheliosis." In order to satisfy those opposed to the latter term, Klemperer [13d] suggested the term "progressive reticulum cell hyperplasia" for just such entities as that under discussion. It appears to us that until more satisfactory evidence than that already offered for dividing and subdividing this group of cases comes forth, it would be less disquieting to resort to some such noncommittal descriptive term as Klemperer's than to attempt to categorize distinctions founded on the questionable significance of minutiae.

The histogenesis of the monocyte as a tissue cell and as a blood cell is a subject concerning which there is considerable divergence of opinion, Forkner [25] having collected as many as nineteen different views on its various phases. However, we shall limit our remarks to one aspect of the subject, namely, the relation between monocytes and vascular endothelium. The tumors in the arterioles of the lungs (figs. 2 and 3) presented a unique opportunity for studying this relation. The masses were situated in the subendothelial space and protruded into the lumens of the vessels. They consisted of monocytic cells morphologically similar to the phagocytic cells seen in adjacent portions of the lung, and they

21. Schultz, A.; Wermbter, F., and Puhl, H.: Eigentümliche granulomartige Systemerkrankung des haematopoetischen Apparates (Hyperplasie des reticuloendothelialen Apparates), Virchows Arch. f. path. Anat. **252**:519, 1924.

22. Siwe, S. A.: Die Reticuloendotheliose: Ein neues Krankheitsbild unter den Hepatosplenomegalien, Ztschr. f. Kinderh. **55**:212, 1933.

23. Van Creveld, S., and Ter Poorten, F. H.: Infective Reticulo-Endotheliosis Chiefly Localized in Lungs, Bone Marrow and Thymus, Arch. Dis. Childhood **10**:125, 1935.

24. Gittins, R.: Anaemia and Reticulo-Endotheliosis, Arch. Dis. Childhood **8**:367, 1933.

25. Forkner, C. E.: Clinical and Pathologic Differentiation of the Acute Leukemias, with Special Reference to Acute Monocytic Leukemia, Arch. Int. Med. **53**:1 (Jan.) 1934.

contained parasites. The side of a tumor nearest to the lumen was covered by a single layer of intact flattened endothelial cells which was continuous with the uninvolved portions of the wall of the vessel. None of the endothelial lining cells showed a tendency to round up and separate from its neighbors and to form free cells. No phagocytosed parasites were seen within these cells. Superficial examination suggested that the two types of cells were identical. However, study of serial sections with special stains led us to believe that there were present two cellular types which were morphologically and functionally distinct, despite their intimacy. This conclusion lends support to the thesis, maintained by one group of observers, that vascular endothelium is highly differentiated tissue and that "the only direction of progressive differentiation with the formation of a new cell type that until now has been demonstrated for endothelial cells is their transformation into fibroblasts." [26] In order to account for the monocytes in the tumor masses this group, headed by Maximow, assumed the possibility that wandering elements may normally be present in small numbers in the subendothelial layer of a blood vessel. In this case it might well be true that these few wandering cells became exuberantly stimulated as a reaction to the presence of the parasites. On the contrary, the supravitalists head the group of those who stated the opinion that vascular endothelium, per se, can and does give rise to a monocytic phagocytic cell, the clasmatocyte.[27] If this were true in this instance, then one would have expected the vascular tumor formation to be a generalized process rather than one limited to the lungs. The purely local nature of the lesions also argues against the term "reticuloendotheliosis," despite which we believe that its judicious use is still useful and desirable.

## SUMMARY

A case of generalized fungous infection (Darling's histoplasmosis) is reported from Missouri, it being the second in which the condition has been observed in an infant and the seventh reported case in the Western hemisphere.

An unusual type of reticuloendothelial hyperplasia in the arterioles of the lungs is described and discussed.

A brief review of disorders of the reticuloendothelial system, especially in infants, is presented.

26. Maximow, A.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 128.

27. Doan, C. A., and Wiseman, B. K.: The Monocyte, Monocytosis, and Monocytic Leukosis: A Clinical and Pathological Study, Ann. Int. Med. **8**:383, 1934.

# SACCHAROSURIA IN AN INFANT

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Saccharosuria is a rare and unusual error of metabolism. Saccharose, ordinary table sugar, is a disaccharide; in the normal digestive process 1 molecule of saccharose is hydrolyzed and split into 1 molecule of dextrose and 1 molecule of fructose. These monosaccharides are then absorbed from the small intestine. There is no significant gastric digestion of saccharose, the principal digestion taking place in the small intestine. The enzyme concerned in this process is secreted into the intestine; it is called saccharase or invertin. Normally saccharose is not found in any of the body fluids, nor is it excreted in the urine.

Most physiologists agree that if excessive amounts of saccharose are ingested, a small proportion may be absorbed unchanged from the intestine. In such cases saccharosuria may occur, as saccharose is not metabolized in the body or utilized directly from the blood stream.

Saccharose will not reduce the ordinary copper reagents used in urinalysis. After hydrolysis, however, both fructose and dextrose will reduce these solutions. Hydrolysis of saccharose is easily accomplished by boiling it in an acid solution, and further identification of this substance is made by polariscopic examination. Saccharose is dextrorotatory, but on hydrolysis the solution becomes levorotatory because of the stronger levorotation of fructose. This solution can further be tested for the presence of fructose and dextrose by means of the formation of osazone, the Selivanoff test and fermentation.

In 1910 Reuss found saccharose in the urine of several infants who were suffering from severe nutritional and gastrointestinal disturbances. He studied the condition in 12 cases and concluded that the saccharosuria was alimentary in origin, being due to the increased intestinal permeability associated with these diseases. He quoted Jaksch, who had shown that this could not be due to the formation of insufficient enzymes in the intestine. Jolles in 1913 reported saccharosuria in a 2 year old child with colic who was fed large amounts of tea and sugar. In 1917 Pi Suñer reported that saccharose was found in the urine after intestinal disturbances, especially in infants. No cases of saccharosuria

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have been reported in recent American or foreign literature, except in 2 instances of pancreatic disease in adults reported, respectively, by Rencki and Falkiewicz and by Hoesch. Numerous reports have described cases in which saccharose was added to the urine. This was done by men seeking to avoid military service, by hysterical women and occasionally by diabetic persons wishing to gain sympathy.

## REPORT OF A CASE

Our patient, a boy 7 months of age, was admitted to the pediatric service on Jan. 23, 1937. He had been well until five days before, when he became feverish and began to cough. On the morning of admission the temperature rose to 105 F., and the respirations became labored and rapid. While at home, the child took fluids well. Orange juice and sweetened drinks were given in large amounts. Shortly before admission, because of the patient's apparent weakness 0.35 cc. of a 1:1,000 solution of epinephrine hydrochloride was injected by the family physician.

There was no family history of diabetes, allergy or tuberculosis. The baby was born at term, weighing 3,330 Gm. He had regularly been breast fed and in addition received about 120 cc. of orange juice and 12 cc. of cod liver oil daily. Administration of cereal had just been started. The child gained well and had no illness. At the age of 4 months he was vaccinated against smallpox.

Physical examination revealed a well developed obese infant who was acutely ill. The temperature was 105 F., the pulse rate 160, the respiratory rate 48, the weight 8,180 Gm. and the sitting height 46 cm. The patient was pale but not cyanotic. The respirations were rapid and deep (of Kussmaul type). There were flaring of the alae nasi and retraction of the suprasternal and the infrasternal notch. The turgor of the skin was fair. The anterior fontanel was not bulging. The abdomen was moderately distended. The heart was normal. Over the upper lobe of the right lung there were dulness and diminished breathing. Scattered over both sides of the chest were many sonorous, sibilant and fine rales. The right ear drum was congested, and a mucopurulent nasal discharge was present. The mucous membranes were dry and red.

Shortly after the child's admission a specimen of urine was obtained. The reaction was acid; tests for albumin and microscopic examinations gave negative results; acetone (4 plus) was present, and 1.8 per cent dextrose was found by Benedict's method. The blood sugar level was 175 mg. per hundred cubic centimeters. The carbon dioxide content of the blood was 22 volumes per cent. Roentgen study of the chest showed pneumonic infiltration in the upper lobe of the right lung. The Wassermann reaction of the blood was negative. Reactions to the Schick, the Pirquet and the Mantoux test were negative. The hemoglobin content was 63 per cent (8.7 Gm.); the red cell count was 3,200,000 and the white cell count 12,500 per cubic millimeter, with polymorphonuclears comprising 56 per cent, lymphocytes 41 per cent and monocytes 7 per cent.

It was believed that the infant was diabetic and had severe pneumonia. He was therefore treated with insulin; subcutaneous injections of saline solution and a transfusion of a small amount of blood were given. The child took 120 cc. of sweetened orange juice and 45 cc. of breast milk or a formula [1] every two hours.

1. The formula consisted of 2 parts of cow's milk and 1 part of a 5 per cent solution of saccharose in water.

The child's general condition improved rapidly and remarkably. The ketosis was soon controlled, and the infection promptly subsided. Small amounts of insulin were given the first three days, because of the small amounts of urinary reducing substance. The remarkable fact was that the blood sugar level remained low. In four days the child's temperature was normal, his lungs had cleared considerably, and his general condition was excellent. The urine, blood sugar level and carbon dioxide content were now normal (table 1). The patient was taking his formula well.

There was considerable difficulty in identifying the small amounts of urinary reducing substance; but it was finally established that this sugar was invert sugar, and at the same time the presence of saccharose was detected. Apparently, then, we had been dealing with an infant who had nondiabetic ketosis as the result of an infection. Incidentally he had saccharose in his urine.

TABLE 1.—*Chemical Findings During Admission Period*

| Date | Blood Sugar, Mg. per 100 Cc. | Carbon Dioxide Content of Blood, Vol. % | Urine | | Insulin Units |
|---|---|---|---|---|---|
| | | | Reducing Substance, Percentage | Acetone | |
| Jan. 23 | 175 | 22.0 | 1.2 | | |
| | 135 | 22.5 | 1.4 | 0 | 13 |
| | 50 | .... | 1.8 | 0 | |
| Jan. 24 | 120 | .... | 0.8-1.2 | 0 | 4 |
| Jan. 25 | 80 | 46.5 | 0.5 (1 specimen) | 0 | 2 |
| | 110 | | | | |
| Jan. 26 | 29 | .... | 0.5-1.0 | 0 | 2 |
| Jan. 28 | 75 | 43.0 | 0 | 0 | 0 |
| Feb. 1 | 55 | 50.5 | 0 | 0 | 0 |
| | Additional chemical findings | | | | |
| Jan. 23 | Urea, 33 mg.; total cholesterol, 120 mg.; chlorides, 640 mg.; total proteins, 8.2 per cent | | | | |
| Jan. 28 | Urea, 10 mg.; total cholesterol, 150 mg.; cholesterol ester, 40 mg. | | | | |
| | Examination of mother's milk showed 2.9 per cent fat | | | | |
| | Examination of mother's, father's and brother's urine showed no reducing substances | | | | |

As soon as the child had completely recovered, we began a series of tests with various sugars to discover the nature of this peculiar error of metabolism. A dextrose tolerance test was performed with 30 Gm. of dextrose given by mouth (3.5 Gm. per kilogram), and a normal blood sugar curve was reported (table 2). A fructose tolerance test done in the same manner also showed a normal blood sugar curve, but saccharose was found in the urine (table 3).

The child was then put on a formula of whole milk and 8.5 per cent lactose. He was also given 60 cc. of orange juice and 12 cc. of cod liver oil daily. While the child received this formula, several sugar tolerance tests were carried out in the following manner: Sixty grams of carbohydrate was dissolved in about 90 cc. of orange juice, and this was substituted for the feeding given at 10 a. m. We then collected specimens of urine until 6 p. m. Because of the child's age and the fact that we were primarily interested in the presence of urinary sugar, further studies of the blood were not made.

When the child was taking the lactose formula, there was saccharose in the urine after the ingestion of fructose and saccharose (table 4).

The formula was then changed to whole milk and 8.5 per cent saccharose. Similar carbohydrate tolerance tests were carried out, and saccharosuria appeared again after the ingestion of fructose and saccharose (table 5).

TABLE 2.—*Results of Dextrose Tolerance Test* *

| Time | Dextrose in Blood, Mg. per 100 Cc. |
|---|---|
| Fasting | 70 |
| ½ hour | 95 |
| 1 hour | 75 |
| 2 hours | 75 |
| 3 hours | 55 |

* The urine contained no sugar.

TABLE 3.—*Results of Fructose Tolerance Test* *

| Time | Fructose in Blood, Mg. per 100 Cc. |
|---|---|
| Fasting | 75 |
| ½ hour | 95 |
| 1 hour | 83 |
| 2 hours | 83 |
| 3 hours | 74 |

* The urine contained 2.90 per cent saccharose, 0.30 per cent dextrose and 0.53 per cent fructose.

TABLE 4.—*Results of Sugar Tolerance Tests with Lacrose Formula*

| Diet | Sugar in Urine, Percentage | | |
|---|---|---|---|
| | Saccharose | Dextrose | Fructose |
| Formula alone | .... | .... | .... |
| Formula with | | | |
| 60 Gm. fructose | 0.10 | 0.18 | 0.48 |
| 60 Gm. dextrose | .... | .... | .... |
| 60 Gm. saccharose | .... | 0.22 | 0.28 |

TABLE 5.—*Results of Sugar Tolerance Tests with Saccharose Formula*

| Diet | Sugar in Urine, Percentage | | |
|---|---|---|---|
| | Saccharose | Dextrose | Fructose |
| Formula alone | .... | .... | .... |
| Formula with | | | |
| 60 Gm. fructose | 0.52 | 0.27 | 0.44 |
| 60 Gm. dextrose | .... | .... | 0.53 |
| 60 Gm. saccharose | 0.53 | 0.88 | 0.23 |
| 60 Gm. maltose | .... | .... | .... |

Determinations of the blood saccharase were made before and after ingestion of 60 Gm. of saccharose. No traces of this enzyme were found in either specimen. However, tests for a normal control child of the same age likewise gave negative results.

At the age of 18 months the patient was again studied. He now weighed 12.7 Kg. His sitting height was 55 cm. His physical development seemed to be

normal, but mentally he was retarded. He did not stand, walk or talk, and his responses did not seem to be normal for his age. At this time he was taking a standard infant diet not unusually rich in carbohydrates. His urine was normal and showed no saccharose. We again collected specimens of urine after adding the various sugars to the child's breakfast. Saccharosuria was present only when the child was given both saccharose and fructose at the same time (table 6).

## COMMENT

As an explanation for this interesting error of metabolism several possibilities suggest themselves. 1. The intestinal mucosa is permeable to saccharose, which is absorbed undigested and excreted as such. 2. The amount of intestinal saccharase is insufficient for the complete digestion of the amount of saccharose ingested. This would then lead to the absorption of some saccharose from the intestine and to its excretion in the urine. 3. The saccharose is synthesized from absorbed monosaccharides and is excreted as such.

TABLE 6.—*Results of Sugar Tolerance Tests With Normal Diet*

| Diet | Sugar in Urine, Percentage | | |
|---|---|---|---|
| | Saccharose | Dextrose | Fructose |
| Normal diet alone | .... | .... | .... |
| Normal diet with | | | |
| 60 Gm. fructose | .... | .... | .... |
| 60 Gm. saccharose | .... | .... | .... |
| 50 Gm. fructose and 50 Gm. saccharose | 0.20 | .... | 0.26 |

The possibility of the absorption of disaccharides from the intestine is mentioned by most physiologists. It has been shown that an infant's intestine can be permeable to unsplit protein molecules, and it is therefore plausible also to assume the occurrence of absorption of disaccharides in infants. Intestinal inflammation or even parenteral infection might make this absorption easier. This explanation of saccharosuria seems most likely to us.

We have no definite evidence of diminution of the amount of saccharase in our patient. When the child is well he seems to be able to care for the inversion of all the saccharose in his formula. In 2 cases of adults with pancreatitis and pancreolithiasis saccharosuria has been ascribed to pancreatic dysfunction or malfunction. The connection of our present observation with a disturbance of pancreatic function has not been established, however.

Synthesis of saccharose seemed to occur when fructose was given while the child was receiving the lactose formula. However, we believe that the saccharose present in the orange juice in which the sugars were dissolved accounted for the small amount of saccharosuria.

It is interesting to note the difference between this case of saccharosuria and other instances of anomalous carbohydrate metabolism

that have been studied in this laboratory. In cases of pentosuria the amount of reducing substance in the urine remains constant and is altogether independent of the diet. The tolerance and metabolism of all carbohydrates in pentosuric patients is entirely normal. With essential fructosuria, the tolerance and metabolism of all carbohydrates except fructose is undisturbed. The addition of as little as 1 Gm. of fructose to the patient's diet gave rise to fructosuria. Fructosuria apparently is due to a deficiency in the mechanism that normally removes excessive fructose from the blood stream.

It seems that saccharosuria occurs only when an excessive amount of saccharose is given or when it is given with other sugars, which compete for prior digestion and absorption. In the presence of infection, either enteric or parenteral, increased intestinal permeability may permit easier absorption of saccharose.

## SUMMARY AND CONCLUSIONS

The case of an infant with saccharosuria during a severe infection of the respiratory tract is reported.

Saccharosuria occurred in this child at the ages of 7 and 18 months when certain combinations of carbohydrates were given.

We believe that saccharosuria is alimentary in origin. It results from either excessive ingestion of saccharose or ingestion of saccharose and of other sugars, which compete with it for prior digestion and absorption.

NOTE.—A detailed chemical study of this case will be published elsewhere in collaboration with Dr. H. Sobotka.

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## BIBLIOGRAPHY

Fischer, A. E., and Reiner, M.: Pentosuria in Children, with Laboratory Data on Four Cases, Am. J. Dis. Child. **40**:1193 (Dec.) 1930.

Hoesch: Spontane periodische Rohrzuckerausscheidung, Klin. Wchnschr. **13**: 275 (Feb. 17) 1934.

Jolles, A.: Ueber den Nachweis der Saccharose im Harn, Biochem. Ztschr. **57**: 420, 1913.

Pi Suñer, A.: Saccharosuria, Siglo méd. **64**:146 (March 10) 1917.

Rencki, R., and Falkiewicz, A.: Ueber einen Fall von Saccharosurie bei Pankreopathie, Klin. Wchnschr. **13**:774 (May 26) 1934.

Reuss, A.: Alimentäre Saccharosurie in Säuglingen mit Darmkrankheiten, Wien. klin. Wchnschr. **23**:123, 1910.

Silver, S., and Reiner, M.: Essential Fructosuria: Report of Three Cases with Metabolic Studies, Arch. Int. Med. **54**:412 (Sept.) 1934.

# DUODENAL PERFORATION IN A NEWBORN INFANT

## TREATED SURGICALLY AND WITH SULFANILAMIDE

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Perforation of the gastrointestinal tract before or shortly after birth not only is rare but is associated with a prognosis so uniformly bad that any therapy which offers hope of saving some of these infants should be of interest. A case is reported here in which the patient survived ten days after operation and died with complications not referable to the gastrointestinal tract, thereby giving us an opportunity to make some pertinent observations.

The patient was referred to us by Dr. Pearl Konttas.

### REPORT OF A CASE

M. D., a girl, was born on Feb. 3, 1938, at 3:30 p. m., of young, healthy parents. A sister aged 4 years was well but had anomalies of her fingers. The birth was normal and occurred without instrumentation or resuscitation. The child was not given gavage or lavage. Nothing unusual was noted at birth, but when feedings were started the infant regurgitated everything. On February 4, twenty-seven hours after delivery, she was given barium sulfate by mouth, and a roentgenogram was taken. This revealed no passage of the barium sulfate beyond the duodenum, and there appeared to be a little free air in the peritoneal cavity. The patient was transferred to the Children's Hospital, a distance of 60 miles, arriving near midnight of the same day. At this time the color was good, the respirations were rapid, the heart rate was rapid, and the abdomen was full although not markedly distended. There was brawny edema of the abdominal wall, particularly of the lower part of the abdomen and the right flank. The infant was slightly jaundiced. By morning her abdomen was distinctly more distended, and the edema and induration had increased. The blood contained 156 per cent hemoglobin; there were 6,050,000 red cells and 2,500 white cells per cubic millimeter with 59 per cent polymorphonuclears and 37 per cent lymphocytes. Fluoroscopic examination showed much free air in the peritoneal cavity and no passage of the barium sulfate beyond the duodenum, except for a small amount which escaped across the lower border of the liver to the right side (fig. 1). A

From the Children's Hospital.

diagnosis of rupture of the duodenum was made, and the patient was taken to the operating room forty-two hours after birth.

During administration of light drop ether anesthesia the abdomen was opened through an upper right rectus incision. All the layers of the abdominal wall were edematous. When the peritoneal cavity was opened a considerable quantity of bile-stained fluid and some air gushed out. Cultures of this fluid were made. The abdominal contents were matted together with bile-stained adhesions, but the bowel itself appeared entirely normal. Without further exploration, the duodenum was exposed. The gallbladder appeared normal. In the anterior wall of the first part of the duodenum, about 2 cm. distal to the pylorus, was found an opening about 1.5 by 0.8 cm., from which poured clear bile and flecks of

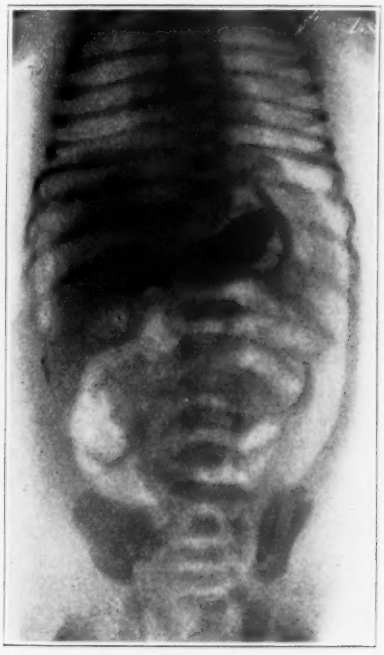

Fig. 1.—Roentgenogram showing the pneumoperitoneum and the escape of barium sulfate to the right flank.

barium sulfate. The edges of the lesion were cleancut and showed no inflammatory reaction. About one third of the opening was sealed off by fibrinous adhesions to an adjacent loop of small bowel. The entire perforation was closed with interrupted silk sutures. The lateral wall of the duodenum at the edge of the ulcer seemed thinned and friable. A free omental graft was placed over the suture line, and the peritoneum was closed without drainage by a continuous silk suture. Fifty cubic centimeters of saline solution was left in the peritoneal cavity. The fascia, subcutaneous tissue and skin were closed with interrupted silk sutures. At the close of the operation 100 cc. of saline solution was given subcutaneously in the axillas. The baby's general condition was fairly good and continued surprisingly good during that day and night.

The following day the patient vomited some material but passed meconium and bile-stained stools. The induration and edema of the abdominal wall had increased and in the right flank almost had the appearance of cellulitis. The swelling extended up over the back and chest. Cultures of material from the peritoneal cavity showed Bacillus coli and nonhemolytic streptococci. Administration of sulfanilamide was started with a subcutaneous injection of 4 grains (0.26 Gm.) in 50 cc. of a physiologic solution of sodium chloride. Lavage was done once; then the patient was given breast milk or an evaporated milk formula every three hours. From this time until her death, ten days later, there was no vomiting. The child took 2 to 3½ ounces (59 to 104 cc.) of food with each feeding; she passed well digested, normal-looking stools, had practically no distention and made a daily gain. Twenty-four hours after administration of the sulfanilamide practically all the edema and induration of the abdominal wall and of the flanks had disappeared. Except for a dusky color of the skin, attributed to the sulfanilamide, the patient's condition seemed remarkably good. Our plan had been to continue the administration of sulfanilamide, after the initial dose, with between 3 and 4 grains (0.19 and 0.26 Gm.) of the drug in divided doses per twenty-four hour period. The patient was therefore given 1 grain (0.06 Gm.) on February 7, and this was repeated six hours later. On February 8 a blood count showed 15,000 white cells with 89.5 per cent polymorphonuclears and a hemoglobin content of 128 per cent. Respirations were rapid and the color of the skin dusky. Because of this color and the fact that sulfanilamide has an uncertain effect on newborn infants, the contemplated dose was not given on this day. On February 9 the color remained dusky, and the temperature had risen to 102 F. On physical examination no definite pathologic change could be found in the chest, but by means of fluoroscopic examination a small patch of pneumonia was found at the apex of the right lung. There was no free air in the peritoneal cavity at this examination.

A blood culture was made, the sulfanilamide content of the blood was determined, and the patient was placed in an open oxygen tent. There was only a trace of sulfanilamide in the blood; the blood culture was positive for B. coli. The infant was given 27 cc. of blood by transfusion, and sulfanilamide therapy was started again, 1 grain in an 0.8 per cent solution to be given hypodermically every six hours. Five hours after the initial dose the concentration in the blood was 1.6 mg. per hundred centimeters, and the next dose was increased to 1½ grains (0.09 Gm.). The abdominal wound, which was dressed at this time, showed no tendency to heal; there was no inflammatory reaction about it. On February 12, 27 cc. of blood was again given by transfusion, and the administration of sulfanilamide was continued by mouth, ⅔ grain (0.04 Gm.) being given every four hours. There were signs of consolidation of both the upper and the lower lobe of the right lung, but while the patient was in the oxygen tent her color remained good. A second blood culture showed B. coli.

On February 14, nine days after the operation, the respirations were definitely labored, and there was clinical evidence of fluid in the right pleural cavity. Fluoroscopic study confirmed this diagnosis.

The right side of the chest was tapped through the sixth interspace in the anterior axillary line, and about 10 cc. of thick, stringy, brick red material was removed with some difficulty through a no. 16 needle.

Smears of this material showed organisms. For this reason and because of the character of the pus it was felt that adequate drainage was necessary. Closed drainage was instituted by means of a no. 16 rubber catheter connected with a

siphon tidal irrigator at the level of the chest. Considerable thick material similar to that aspirated by needle was drained out during the next few hours, and the baby's breathing was somewhat improved. After about three hours, however, air began draining continuously through the apparatus, breathing was embarrassed, a moist cough appeared, and pneumothorax was present on the right. The irrigator was lowered well below the level of the chest to avoid aspiration of fluid through the evident bronchial fistula. It was felt that we were dealing with gangrene of the lung, which, when the necrotic débris was washed away by several hours of irrigation, gave rise to multiple bronchial openings, while the consolidated lung was unable to expand even as air was removed by the drainage. Cultures of the pus revealed B. coli.

The patient died on February 15, at the age of 12 days.

The blood cultures, determinations of sulfanilamide and transfusions were made with a minimum of disturbance to the child by Dr. Janet Baldwin, resident in pediatrics.

It was unfortunate that an autopsy was not permitted. It would have been especially interesting to see whether or not the duodenal wound had healed. We know, however, that the intestinal tract functioned well up to the time of the patient's death, and twenty-four hours before this no free air could be demonstrated in the peritoneal cavity by fluoroscopic examination. The abdominal wound, however, showed no tendency to heal, and it is possible that the duodenal wound was behaving similarly, with adhesions preventing the escape of intestinal contents and air into the peritoneal cavity.

## COMMENT

In retrospect this case has many interesting aspects. The early administration of barium sulfate for roentgen study not only made possible the diagnosis of the ruptured viscus but showed the perforation to be situated in the duodenum. The child was in a condition that justified an attempt at surgical repair. De Vel [1] has called attention to the ease with which pneumoperitoneum can be diagnosed by roentgen examination; the addition of barium sulfate in our case determined the site of rupture, thus facilitating the work of the surgeon. The edema and induration of the abdominal wall suggested sepsis, and the culture of B. coli from the peritoneal exudate further substantiated this impression. Treatment with sulfanilamide was tried hopefully. The improvement following its administration, apparent both in the general condition of the infant and particularly in the prompt disappearance of the edema and induration, was quite as convincing as that seen when erysipelas of infants is treated with this drug (note the temperature curve, fig. 2). The cyanosis following the use of sulfanilamide confused us and led to its discontinuance until it was recognized that the cyanosis was due to pneumonia. The positive blood cultures were somewhat surprising at the stage of recovery obtained,

1. De Vel, L.: Intestinal Perforation with Pneumoperitoneum in the Newborn Infant, Am. J. Dis. Child. **45**:587-589 (March) 1933.

since there was no evidence of sepsis at the time. It should be reiterated that B. coli was found in the peritoneal cavity, in 2 blood cultures and in the pleural fluid.

Although perforation of the gastrointestinal tract of an infant is rare [2] and is even more unique when delimited to the gastric or duodenal area or to the newborn period, the cause of the condition may be the same in a variety of cases, regardless of location or time of occurrence. Discussion therefore should not be limited to any one type but should include a survey of all gastrointestinal ulcerations with or without hemorrhage or perforation, and it probably should extend to other forms of infection of the newborn which may be due to sepsis or metastasis, not necessarily ulcerative.

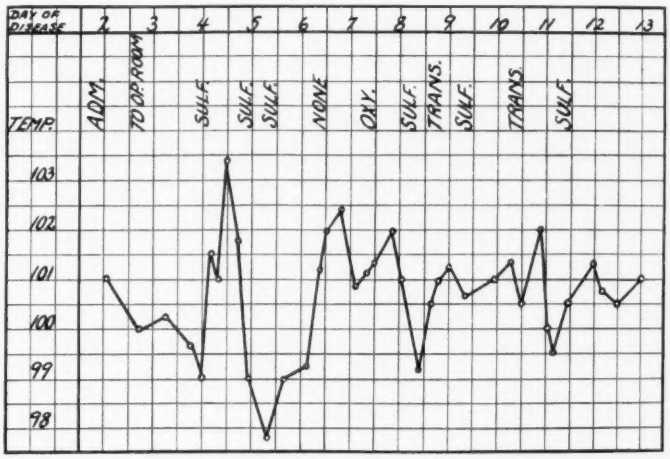


Fig. 2.—Chart showing the relation between the temperature curve and therapy.

Since this infant postnatally had almost forty-eight hours in which to become infected with bacteria, it is impossible to prove that sepsis originated the train of symptoms; but in reconstructing this case and in reviewing the literature on enteritis, ulcerations and perforations of newborn babies we think it highly probable that bacterial invasion played the major and original role here and that it preceded ulceration and perforation. Infection probably plays a much more significant role in the pathologic conditions of the newborn infant and of the fetus than is generally appreciated. The chief reason for not recognizing infection in the newborn is that it does not cause the signs of inflam-

2. (*a*) Holt, L. E.: Duodenal Ulcers in Infancy, Am. J. Dis. Child. **6**:381-393 (Dec.) 1913. (*b*) Abt, I. A.: Fetal Peritonitis, M. Clin. North America **15**:1, 1931. (*c*) Dunham, E. C., and Goldstein, R. M.: Rupture of the Stomach in the Newborn Infants, J. Pediat. **4**:44-50, 1934.

mation, local or general, which are usually associated with infection in children or in adults. The fetus or the newborn child at times behaves toward bacteria more like a culture medium than like a living organism mobilizing to fight an invader; bacteria grow in it as though in vitro instead of in vivo. This is not a unique observation; attention has been called to it repeatedly. Dunham [3] in her reports on sepsis in infancy mentioned several instances of peritonitis and meningitis noted at autopsy but not suspected during life. Dunham and Shelton,[4] Holt [2a] and Helmholz [5] noted that gross and microscopic examination of ulcerations of the gastrointestinal tract of newborn infants showed absence of inflammatory reaction. When the tissues have been examined microscopically for bacteria, the presence of organisms has usually been noted. In reviewing the case reports of gastrointestinal ulceration and perforation in the newborn we concluded that the occurrence of edema,[6] spots of gangrene [7] and various other atypical symptoms suggests, in view of our findings, sepsis in these cases also.

Little is known about the immune mechanism during any time of life, and certainly a minimum is known about it at birth. What happens when a sterile organism such as a fetus first encounters bacteria? How often is there invasion of the blood stream at this stage without evidence of disease from it? How often is immunity established without serious consequence in spite of it? What factors may influence the establishment of normal immunity? In those who survive the newborn period there is wide variation in ability to cope with different types of infection; it is therefore logical to assume that a certain percentage will be so lacking that they succumb shortly after birth from inability to handle ordinarily harmless bacteria.

There are many factors that may influence the response of the fetus or the newborn child to the contact with bacteria. Infection in the mother during pregnancy has been known to result in sepsis of the newborn infant. It has been reported in cases of syphilis, smallpox and typhoid as well as of streptococcic and pneumococcic infections. A study of the relation of placentas and newborn babies [8] revealed con-

3. Dunham, E. C.: Septicemia in the Newborn, Am. J. Dis. Child. **45**:229-253 (Feb.) 1933.

4. Dunham, E. C., and Shelton, M. T.: Multiple Ulcers of the Stomach in a Newborn Infant with Staphylococcus Septicemia, J. Pediat. **4**:39-43, 1934.

5. Helmholz, H. F.: Duodenal Ulcers in Infancy, Arch. Pediat. **26**:661, 1909.

6. Seinsheimer, F.: Duodenal Ulcer with Rupture on the Fourth Day of Life, J. A. M. A. **105**:875-876 (Sept. 14) 1935.

7. Brockington, C. F., and Lightwood, R.: Duodenal Ulcerations in Infants, Lancet **2**:1209-1210, 1932.

8. Adair, F. L., and Thelander, H. E.: A Study of the Weight and Dimensions of the Human Placenta in Relation to the Weight of the Newborn Infant, Am. J. Obst. & Gynec. **10**:3-36, 1925.

ditions of the placenta which may be significant, such as infarcts, partial separation, placenta praevia and premature rupture of membranes. At birth, prolonged or difficult labor, asphyxiation, trauma or drugs administered to the mother may affect the immunity of the child. Injections of whole blood, now given almost routinely in many hospitals to infants born with difficult labor or suffering from asphyxiation, may be more important immunologically than hematologically.

## SUMMARY AND CONCLUSIONS

A diagnosis of duodenal perforation was made for an infant 1 day old. She was operated on and treated with sulfanilamide but died on the tenth postoperative day with sepsis due to B. coli, empyema and bronchial fistula, the gastrointestinal tract functioning normally after the repair up to the time of death.

In gastrointestinal symptoms of newborn babies indicating obstruction, roentgen study after the ingestion of barium sulfate should be done early to facilitate the diagnosis of the type and the situation of the lesion.

In case of perforation, if the condition of the child warrants it, surgical intervention should be attempted.

Even with the lack of the usual symptoms and reactions of infection, sepsis should be suspected. The peritoneal contents should always be cultured, and blood cultures should be made more frequently than is the custom at present.

Sulfanilamide was well tolerated by this infant and should be used if the organism is susceptible to the drug.

Transfusion should be tried. It may benefit chiefly through conferring adult immune properties.

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# Progress in Pediatrics

## DIABETES INSIPIDUS IN CHILDREN

### A CRITICAL REVIEW OF ETIOLOGY, DIAGNOSIS AND TREATMENT, WITH REPORT OF FOUR CASES

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Diabetes insipidus is a symptom which may be due to a variety of causes. Its diagnosis and treatment, unsatisfactory as the latter may be, present no difficulty, but the detection of the underlying cause often requires considerable study and may at times be impossible. When this underlying cause is not ascertainable a diagnosis of idiopathic diabetes insipidus may be made. In many instances this classification will be correct, since neither the further course nor the necropsy will reveal an anatomic cause for the polydipsia and polyuria. In other cases the basic process will be recognized only after the symptoms have progressed for months or years.

The observation of a few cases of polyuria and polydipsia and the attempt to formulate their prognoses induced us to study the literature of diabetes insipidus in children. This survey demonstrated that definite progress has recently been made in the understanding of some of the etiologic processes underlying this condition and also that its classification as well as the evaluation of its symptomatology should be reconsidered. No attempt has been made to compile all the reported cases of diabetes insipidus. Each section is summarized, so that a final summary appears to be unnecessary.

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In this paper considerable space has been given to therapy with extracts of the posterior lobe of the pituitary gland. There is much confusion in the terminology employed by various authors in regard to these extracts. This arises partly because much of the material quoted was written before a distinction had been made between pitressin and pitocin. It is possible that some of the experimental studies and clinical results are confused because proper extracts were not employed. In this review an attempt has been made to specify the type of extract administered and when possible to use the terminology employed by the respective authors. Obviously the active antidiuretic substance is pitressin.

PATHOGENESIS

The pathogenesis of diabetes insipidus is not completely understood.[1] Postmortem studies early directed attention to the region of the pituitary gland and the adjacent nerve centers in the floor of the third ventricle (Erdheim). It would appear that the hypophysis and the diencephalic region not only are closely related anatomically but constitute a functional unit (Biedl). Thus far attempts to attribute diabetes insipidus to any single part of this system have failed of general recognition.

The theory that disturbance of the posterior lobe of the pituitary gland is operative in causing the symptoms of diabetes insipidus is based on evidence obtained experimentally, clinically and at necropsy.[2] It is best supported by the fact that in the majority of cases the symptoms disappear or are modified after administration of extracts of the posterior lobe of the pituitary gland.[3] There are instances, however, in which lesions of the nerve centers have been discovered but in which the pituitary gland was not affected (Raab). Furthermore, it has been demonstrated experimentally that cauterization of the floor of the third ventricle causes the symptoms of diabetes insipidus in animals whose pituitary glands have been left intact.[4] Still other experiments have shown that removal of the pituitary gland is followed by transitory polyuria only and that after renal function is restored to normal injury to the tuber cinereum leads to permanent diabetes insipidus. These observations have suggested that the nerve centers of the floor of the third ventricle are primarily at fault.

The theory that either the pituitary gland alone or certain cerebral centers alone are at fault is not inconsistent with the facts, and attempts have been made to bring apparently divergent theories into accord by assuming a close functional interrelationship between the pituitary gland and the neural centers of the diencephalon. It has been shown that nerve fibers connect the nucleus supraopticus and the nucleus paraventricularis of the diencephalon with the posterior lobe of the pituitary gland, and many experimental observations have demonstrated that the diencephalon exerts an influence on the pituitary gland.[5] The conclusion, therefore, appears attractive that water metabolism is regulated through a neural mechanism by the nuclei of the floor of the third ventricle, and much

1. Bailey and Bremer; Cushing, 1913, 1912 and 1932; Leschke; Peters; Raab; Ranson; Sato; Verney.

2. Cushing, 1912 and 1932; Marañon.

3. Farini; Farini and Ceccaroni; von den Velden.

4. Camus and Roussy; Houssay.

5. Fisher and Ingram; Fisher, Ingram and Ranson; Fisher, Ingram, Hare and Ranson; Futcher, 1931; Greving; Pines.

evidence suggests that the nucleus supraopticus plays an important part in this (Fisher, Ingram and Ranson, 1938).

On the other hand, there exist a number of observations which suggest that the secretions of the pituitary gland (regulating water metabolism) find their way into the diencephalon and the cerebrospinal fluid.[6] It has been thought that the Herring bodies are secretory products of the intermediate part of the pituitary gland which travel through intercellular canals in its posterior lobe to reach the cavity of the infundibulum.[7] The portal circulation of the pituitary veins is another probable pathway by which pituitary products may be carried into the diencephalon (Popa and Fielding). Thus it could be assumed that the hormone of the posterior lobe of the pituitary gland becomes effective by way of the diencephalic centers. Postmortem reports of cases of diabetes insipidus have not helped greatly to solve this problem, since there are instances on record (Fink) which can be used in favor of any theory one may wish to support.

In view of this controversy it must be stated at the present time that the symptoms of diabetes insipidus cannot be attributed to any one part of the diencephalopituitary system. It may be assumed that there appears to exist a continuous exchange of neural and hormonal stimuli between the posterior lobe of the pituitary gland and the diencephalon and that these structures constitute a functional unit. Disturbance of either part of this cooperating mechanism may cause diabetes insipidus. However, it should be borne in mind that morphologic as well as physiologic studies have shown that the cells of the nuclei of the tuber cinereum manifest secretory activity and that these possibly substitute under certain conditions for a deficiency of the posterior lobe of the pituitary gland.[8]

The pathways taken by the central stimuli to the periphery are still undetermined. Arguments have been presented in support of a theory of neural regulation. The inefficacy of extracts of the posterior lobe of the pituitary gland in anesthetized animals[9] and their diuretic action when administered[6] intracisternally have led to the conception that the hormone of the posterior lobe of the pituitary gland acts on certain cerebral centers in the sense of an antidiuresis; from these centers the water metabolism is said to be regulated by purely neural pathways. However, experiments (Janssen) showing that an extract of the posterior lobe of the pituitary gland continues to exert its antidiuretic effect in an animal from whom the cervical or thoracic portion of the

6. Deleonardi; Jánossy.
7. Cushing, 1933; Herring; Scharrer and Gaupp.
8. Sato; Scharrer and Gaupp; Trendelenburg.
9. Adolph and Ericson; Molitor and Pick.

spinal cord has been removed tend to disprove this theory. It has also been shown that the isolated kidney, which ordinarily produces diluted and hypotonic urine, will secrete more concentrated urine after the addition of an extract of the posterior lobe of the pituitary gland to the perfusion fluid (Starling). Such results as these appear to indicate that the pituitary secretion acts directly on the kidney (Sajous) and enables this organ to reabsorb water in the tubules.[10] Many authors, therefore, have expressed the opinion that diabetes insipidus is a pathologic condition caused by a lack of the antidiuretic principle of the pituitary gland (pitressin) (Kamm).

On the other hand, diabetes insipidus has also been considered to be due to the action of direct diuretic stimuli.[11] Although this theory has few adherents, the possibility that a diuretic hormone is secreted by the anterior lobe of the pituitary gland deserves mention. The hypothesis is based on the following considerations and experiments. As a rule complete destruction of the hypophysis does not cause diabetes insipidus in man. This fact led to the assumption[12] that destruction of the neurohypophysis results in diabetes insipidus only when the anterior lobe is left functionally intact. Experimentally, well established polydipsia in a dog was eliminated by complete hypophysectomy (Keller). Several months later, when an extract of the anterior lobe was administered to this animal, a marked increase in the intake of water was noted. This polydipsia lasted for twelve days, after which resistance to the extract seemed to develop. It was then concluded that the pars anterior plays its role through the thyroid gland, the thyrotropic principle being the connecting hormone. This supposition is also supported by the fact that diuretic extracts of the anterior lobe have been made inactive by removal of the thyroid gland.[13]

The diuretic effect of the thyroid hormone has often been emphasized (Eppinger), and the statement has been made that it acts directly on the kidney (Biasotti). A report of the termination of symptoms in a case of diabetes insipidus after development of myxedema in a child (Strauss) has contributed to the theory that the thyroid gland may play a part in the pathogenesis of diabetes insipidus, and it is not surprising that thyroidectomy has been considered as a method of its treatment. Experiments in dogs have been reported in which diabetes insipidus was cured by removal of the thyroid gland and produced again by the peroral administration of thyroid preparations.[14] In fact a marked,

10. Iversen and others; Peters.
11. Bourquin; Grassheim.
12. von Hann; Richter; Richter and Eckert.
13. Barnes and others; Biasotti.
14. Mahoney; Mahoney and Sheehan.

though temporary, amelioration of symptoms in a patient with diabetes insipidus was observed after removal of an adenoma of the thyroid gland (McConnell), and an increased reactivity to pitressin after thyroidectomy was also observed.[15]

*Summary.*—In accord with present knowledge, it must be concluded that the symptoms of diabetes insipidus are caused by the lack of a hormone from the posterior lobe of the pituitary gland. The hormone's mode of action, however, and its transmission to the peripheral organs concerned with water metabolism have not yet been explained.

## PATHOLOGIC PHYSIOLOGY

The cause of polyuria, the most constant symptom of diabetes insipidus, has been the subject of much investigation and speculation. In one of the earliest theories, that of Tallqvist and Meyer, it was maintained that in cases of diabetes insipidus the kidneys had lost their ability to concentrate and hence abnormal amounts of water were required to eliminate the solids of the urine. This theory, however, was not generally accepted.[16] It has been shown that in certain cases of true diabetes insipidus the kidneys can produce concentrated urine, and in many cases the concentrating power of the kidneys becomes demonstrable during fever or anesthesia. While the addition of sodium chloride to the diet is sometimes followed by the passage of large amounts of urine with little increase of its concentration, in other instances a definite urinary concentration takes place (Salmonsen). This concentration is not impressive when the absolute percentage of sodium chloride found in the urine is considered, since this will be low as long as large quantities of water are excreted. However, the amount of sodium chloride excreted as compared with the value found before the administration of sodium chloride may show a considerable relative increase. In the case reported by Forschbach and Weber an increase of the urinary chlorides from 0.038 to 0.28 per cent was observed. Although the latter value is still absolutely low, it represents an increase of 637 per cent from the basic value, thus in fact demonstrating a better concentration than that usually observed in normal persons under the same experimental conditions. Kennaway and Mottram found that in diabetes insipidus urea was four times more concentrated in the urine than in the blood. While it is true that in the urine of a normal person the urea is 60 to 80 times more concentrated than in his blood, it cannot be denied that a certain ability to concentrate

15. Findley; Findley and Heinbecker.

16. Finkelnburg; Fitz; Forschbach; Forschbach and Weber; Oehme and Oehme; Salmonsen.

can be shown in diabetes insipidus also. These observations were not compatible with the original theory of Tallqvist and Meyer, and it became obvious that the assumption of primary renal hydrorrhea would explain the observations on diabetes insipidus better than the theory of a loss of concentrating power of the kidney; that is to say, the increased excretion of water is the primary factor, while the low content of solids of the urine, instead of being the cause of the disease, is to be considered a secondary result of the polyuria (Salmonsen). The abnormal permeability of the kidney may be due to a lack of antidiuretic substance (pitressin), which is probably necessary for the reabsorption of water in the loops of Henle (Burgess, Harvey and Marshall).

These two theories have been combined, and now, according to Leschke, diabetes insipidus is to be considered a functional disturbance in which an increase of water diuresis and an inhibition of molar diuresis are simultaneously present.

According to Lichtwitz (1911) and Lichtwitz and Stromeyer (1914), not all the elements of the urine are affected equally by the excretory inability of the kidney. While nitrogen and phosphate are supposed to be excreted normally, this is not true of sodium chloride. When Salmonsen made the statement that sodium chloride was excreted more rapidly in the presence of diabetes insipidus than under normal conditions, the question of selective inability of the kidney was made the subject of a study by Haymann and Fanconi. They tried to discover the substance at fault by experiments in which fluids were withheld and by the feeding of various substances, such as phosphates, urates, excessive acids and organic acids. They did not succeed, however, in finding any substance showing particular resistance to renal elimination.

Veil differentiated between a hyperchloremic-hypochloruric form of diabetes insipidus and a hypochloremic-hyperchloruric type. The latter can be produced experimentally by a lesion of the fourth ventricle (Bernard), while a lesion of the diencephalon is supposed to cause hypochloruric diuresis. These two types have also been differentiated in human beings, and it has been stated that the hyperchloremic-hypochloruric form is the type usually found. It is supposed to comprise those cases in which thirst is tolerated badly and in which concentration of the blood and loss of weight occur when water intake is restricted. In such cases response to pitressin is favorable. On the contrary, it has been stated that in cases of the hypochloremic-hyperchloruric type thirst is better tolerated and is not associated with loss of weight and, furthermore, pitressin has no effect. This differentiation is not valid in every case in human beings, and the transition of one form into the other has been observed.

In an effort to obtain a better understanding of the pathologic physiology of diabetes insipidus, patients have been subjected to abnormal experimental conditions; in some cases water was withheld, and in others large amounts of sodium chloride were administered. After extreme limitation of fluid the concentration of urine is only moderately increased (specific gravity of 1.007 to 1.010), while under the same conditions the urine of a normal person or of a patient suffering from primary polydipsia (habitual polydipsia in neuropathic children) reaches a specific gravity of about 1.030. However, in the examination of the blood before and after the limitation of water, an increase of the molar concentration in the latter period was noted by Leschke, while Christie and Stewart found the same electrical conductivity in the two periods. Reports of the amounts of chlorides in the blood during restriction of water are contradictory, and the uremia noted by Leschke has not been observed by other investigators (Haymann and Fanconi). These experiments, therefore, have not contributed to the explanation of the abnormal physiology of diabetes insipidus. While fluid is being withheld, the diuresis of water continues. Since the water excreted is derived from the tissue, a loss of turgor of the skin and a loss of body weight may be expected in these patients. Within a few hours losses of from 2 to 3 Kg. have been observed (Veil).

In all cases of diabetes insipidus the percentage of sodium chloride in the urine remains below that of the blood. Beumer made this the basis of a functional test for diabetes insipidus, as follows: Fluids are restricted, and 3 to 5 Gm. of sodium chloride is given by mouth. The chloride content of the hourly portions of urine is then determined. In the presence of diabetes insipidus the percentage of chlorides in the urine will constantly remain below that of the plasma.

For a better understanding of the abnormal physiology of diabetes insipidus it is evidently necessary to consider more than the kidney; the processes in body tissues must be investigated. Emphasis has been placed on a disturbance of the water and salt exchange between the blood and the tissues (Veil, 1923). This factor certainly deserves further attention. An attempt might be made also to answer the question whether changes in blood electrolytes parallel changes in urinary excretion of these substances, both with and without treatment by the administration of pitressin. The colloidal osmotic pressure of the blood proteins has been found by Baráth and Weiner to be definitely increased and has been considered to be the cause of an augmented stream of fluid from the tissues into the blood. Marinesco and his co-workers (1930) claimed to have demonstrated a slight increase of acidity of the tissues in diabetes insipidus.

*Summary.*—In diabetes insipidus the kidneys have a decreased ability to concentrate such substances as sodium chloride and urea, although this capacity is not entirely lost. The exchange of water and salt between blood and tissues needs further investigation.

## ETIOLOGIC CLASSIFICATION

Considerable difficulty is encountered in an attempt to classify the reported cases of diabetes insipidus in children. Many of them were observed for only a short period, and in the absence of typical associated symptoms a diagnosis of the underlying process was not made. Frequently, therefore, the condition has been listed as idiopathic when continued observation, operation or necropsy might have determined the underlying pathologic process. It is more accurate to note the doubtful forms as "unclassified," reserving the term "idiopathic" or "idiopathic-hereditary" to designate the hereditary forms and some types caused by developmental defects. The cause in some cases appears to be trauma; in others there may be responsible an acute infectious process, and in still others, a chronic process, such as tuberculosis, syphilis or xanthomatosis. Tumors will be considered as a separate factor, although in some instances they might be included with the group of developmental defects. Finally, a few rare conditions will be classified in a special group. The following etiologic classification of diabetes insipidus is suggested:

1. Idiopathic-hereditary
2. Due to trauma
3. Due to encephalitis
4. Due to tuberculosis
5. Due to syphilis
6. Due to xanthomatosis
7. Due to tumor
8. Due to rare etiologic factors
9. Unclassified

## IDIOPATHIC HEREDITARY DIABETES INSIPIDUS

In Adolf Weil's classic description, he gave a detailed account of four generations in a family consisting of 91 persons, 23 of whom suffered from diabetes insipidus. Weil's son, Alfred, continued these studies over a fifth generation of this family and found among 220 members a total of 35 in whom diabetes insipidus developed. Hereditary transmission from a parent to an offspring was direct in all but 1 instance. Of all of the children of affected parents, more than one half

of the boys and one third of the girls suffered from the disease. Polyuria and polydipsia, while probably present at birth in these cases, were noticed definitely during the second year. The thirst increased as the age advanced and usually reached its height between the twentieth and the thirtieth year. A slow improvement took place after the age of 50 years, but the affected persons retained their abnormality for life. A few days before death the symptoms ceased. It was repeatedly observed that during periods of fever the symptoms disappeared and the specific gravity of the urine was as high as 1.018. By adding 12 Gm. of sodium chloride to the regular diet of one of these patients it could be shown that the kidneys had not lost their ability to concentrate. The abnormal water metabolism did not affect the general health, and the patients carried on their usual occupations without much difficulty. There were no complaints of headache or vertigo. The family was free from mental disorders, neuroses and alcoholism. The digestion was normal. Although in many cases the diet consisted chiefly of bread and potatoes, a satisfactory nutritional state was maintained. The circulatory system showed no abnormalities, the heart was not hypertrophied, and arteriosclerosis did not develop in the older members of the family. The sexual functions were normal, and the fecundity of the family was above the average. No difficulties were encountered by the affected women during pregnancy and delivery. There was no special predisposition to any particular disease. The course of contagious diseases in the children did not differ from that in normal children. Three members of this family had syphilis; this was certainly not etiologically related to the diabetes insipidus (see the section entitled "Diabetes Insipidus Due to Syphilis"). Physical development was normal. The only developmental defect in this family was polydactylism in 1 child, but he did not suffer from diabetes insipidus. Some of the affected people lived to such ages as 83, 87 and 93 years.

In addition to the family just described there have been others in which diabetes insipidus appeared to be hereditary. Bulloch, in 1909, published the pedigrees of 13 affected families, and a more recent critical review on this subject in 1935 by de Lange (1935) included 21 families.[17] There can be no doubt that the hereditary form is more frequent than Lange's report indicates because to this can be added the reports of Mensi, Peterman, Sugimoto and Levit and Pessikova.

In the family described by the Weils the ratio of the affected to the healthy siblings was such that diabetes insipidus could be considered a dominant hereditary character (Just). No generalizations, however,

17. Chase; Chester and Spiegel; Clay; Deebrey; Ehrmann; Gänsslen and Fritz; Gee; Janzen and Broekman; Knöpfelmacher; Lacombe; Lauritzen; McIlraith; Marinesco; Martinez and Navarron; Orsi; Pain; Reith; Sasse; Wachsmuth; Adolf Weil.

can be made. Levit and Pessikova examined 16 cases of "idiopathic" diabetes insipidus and found only 3 cases in which it was familial. In 2 of the families concerned only 2 members had the disease. It is evident, therefore, that idiopathic diabetes insipidus cannot always be a dominant hereditary character. The observation has been made that in several families members of one generation may escape the condition.[18] Both males and females are affected, although, as previously stated, a greater number of males with the hereditary form have been reported. Transmission may take place through either the paternal or the maternal side. Consanguinity was present in only 2 families.[19]

The nature of hereditary diabetes insipidus can only be speculated on. No reliable reports of necropsies are available, and therefore the pathologic changes underlying this form of the disease are known. Adolf Weil suggested that there are hereditary morphologic abnormalities of certain parts of the nervous system. According to present understanding of the pathogenesis of diabetes insipidus, these hereditary abnormalities should involve the diencephalopituitary region.

Mention should be made of the fact that some patients or families with hereditary diabetes insipidus also present other physical defects and sometimes neuropathic and psychotic abnormalities (Eichhorn). Ehrmann described 3 brothers who had polydipsia and polyuria from infancy and who were also mentally deficient. Of the 3 brothers reported on by McIlraith, "infantile fits" occurred in 2 until they reached the age of 3 years; they both were mentally retarded, and 1 had a speech defect. In the family described by Knöpfelmacher an afflicted boy 8 years of age had marked congenital ichthyosis. Several cases belonging in the group of the so-called Laurence-Moon-Biedl syndrome (Reilly and Lisser) should also be mentioned. This syndrome consists of a multiplicity of developmental defects, such as obesity, hypogenitalism, mental retardation, retinitis pigmentosa, syndactylism and polydactylism. We have pointed out (1937), however, that too sharp a demarcation of this syndrome should not be made, since in many cases the syndrome is incomplete or associated with defects not included in the original description. Included among the additional symptoms occasionally observed is diabetes insipidus. Bernhardt described 2 brothers, both of whom showed obesity, hypogenitalism and mental retardation. The older brother had retinitis pigmentosa and suffered from thirst. The younger brother drank a great deal of water and voided every half hour, the daily output amounting to 3 to 5 liters. Bailey and Bremer mentioned a boy 17 years of age in whom diabetes insipidus was associated "with polydactylism and other signs of degeneration." In the

18. Clay; Gee; Reith; Wachsmuth.
19. Chester and Spiegel; Adolf Weil.

descriptions of certain other cases of the Laurence-Moon-Biedl syndrome, there is mention of polydipsia or polyuria.[20] A sibling of Denzler's patient had a "split vertebral column." "Traumatic" diabetes insipidus was seen in a patient with a harelip (Drouet, Vérain, Grandpierre and Pierquin). In our case 3 the patient's sister, 7 years of age, was 20 pounds (9.1 Kg.) overweight and manifested obesity of the Fröhlich type, and a cousin of the father had a harelip.

The occurrence of developmental defects in patients with diabetes insipidus or in members of their families may be used as an argument in favor of the theory that an inherited morphologic abnormality is the basis of certain familial forms of diabetes insipidus. It is questionable, however, whether this is true in all cases of the hereditary type.

Chester and Spiegel found that solution of posterior pituitary was effective in the treatment of their patients with hereditary diabetes insipidus, while in one of Bailey and Bremer's cases this extract ("pituitrin, Parke, Davis & Co.") was not beneficial.

*Summary.*—Diabetes insipidus may be hereditarily transmitted, sometimes apparently as a dominant characteristic. This form of the condition affects more males than females; polydipsia and polyuria appear in early infancy and last throughout life; health, resistance to disease and longevity are unaffected. Transmission may take place through either the maternal or the paternal side. In some cases diabetes insipidus of the hereditary type is associated with physical and mental defects, among which should be mentioned the Laurence-Moon-Biedl syndrome. The basis of the pathologic changes of hereditary diabetes insipidus is unknown.

### TRAUMATIC DIABETES INSIPIDUS

Diabetes insipidus following injuries of the head has been repeatedly reported; it appears to occur more frequently than post-traumatic diabetes mellitus (Stern). Zenker observed diabetes insipidus 4 times in 2,800 cases of injury of the head. The incidence was higher in cases of basal skull fracture, 3 of his 4 cases occurring in 250 cases of such fracture. Since lesions in the region of the pituitary gland or in the neural structures contiguous to it lead to diabetes insipidus, it is probable that basal skull fractures cause the condition either by hemorrhage or by the formation of scar tissue in the diencephalopituitary region. Projectiles located in this area have furnished the evidence that a center for water metabolism is present in the tuber cinereum or in the posterior lobe of the pituitary gland.[21] In the category of trauma are those cases in which it was reported that a fall downstairs or from a chair or a swing was the inciting factor of diabetes insipidus. It

20. Denzler; McCrae and Weiss; McKinney; Madigan and Moore.

21. Frank; Marañon and Pintos.

must be remembered, however, that in cases in which the condition was later shown to be due to tumor or xanthomatosis the onset has often been traced to such accidents. A history of trauma, therefore, should not prevent the search for other causes. In psychopathic persons so-called primary polydipsia may follow trauma, and the differential diagnosis between it and true diabetes insipidus may then present great difficulties.

Usually when diabetes insipidus has followed injury of the head the latter has been severe. Concussion of the brain with loss of consciousness has been reported in the majority of such cases. The interval between the injury and the appearance of symptoms of diabetes insipidus varies; in some instances the patient complains of intense thirst immediately after recovering consciousness,[22] and in others the symptoms appear only after one or more months.[23] The duration of the symptoms cannot be predicted, since in some instances there is recovery after a short time, while in others the condition is permanent. Not infrequently the polyuria and polydipsia gradually disappear as the child grows older,[24] but recurrences have been reported in some of these cases (Zenker).

The intensity of the polyuria and polydipsia is sometimes marked in cases of traumatic diabetes insipidus, ingestion and excretion of 7 to 8 liters of fluid daily being not uncommon. Fever may cause improvement of these symptoms (Leschke) but not consistently. Obesity and arrest of sexual development may accompany the disease in some cases;[25] on the other hand, loss of weight and normal sexual development have been reported. Perspiration is frequently reduced. Involvement of the cranial nerves has often been observed, and deafness has been reported (Chavanis).

In the majority of cases roentgenograms of the skull reveal no pathologic changes, although projectiles may, of course, thus be readily located. In one of Leschke's cases there was a thickened bony ridge extending from the parietal bone to the base of the skull.

In cases of traumatic diabetes insipidus the effect of extracts of the posterior lobe of the pituitary gland on the polyuria and polydipsia is not uniform. For example, Marañon and Pintos reported a marked reduction of the urinary output after the injection of pituitary extract, while in J. H. Turner's case the results must be considered doubtful. Koral reported a case in which "extract secale cornutum and decoct. chim.c.op." (extract of ergot and decoction of chimaphila with opium) were con-

22. Charcot; Leschke.
23. Marañon and Pintos; J. H. Turner.
24. Delpierre; Leschke; Mosler; J. H. Turner.
25. Engel; Marañon and Pintos.

sidered efficacious. Short wave treatment of the tuberopituitary region was stated to be of value in 1 case of diabetes insipidus and mild diabetes mellitus caused by trauma (Drouet, Vérain, Grandpierre and Pierquin).

*Summary.*—Diabetes insipidus may follow trauma to the head, presumably as a result of pathologic changes in the diencephalopituitary region. Since a history of trauma to the head is so common in children, it should not obviate search for other causes for polyuria and polydipsia. Symptoms may appear shortly after the trauma or not for several months; they may be temporary or permanent; they may be accompanied by such other manifestations of damage to the midbrain as obesity and hypogenitalism; they may or may not be benefited by administration of pitressin.

### DIABETES INSIPIDUS DUE TO ENCEPHALITIS

Presumably it is encephalitis as a sequel of influenza, measles, scarlet fever, pertussis, diphtheria, chickenpox or vaccination which produces symptomatic diabetes insipidus in the cases included in this section. It has been observed also after epidemic encephalitis and "chronic" encephalitis in children, adolescents and young adults (Snell). Hall's patient was 16 years old when he had encephalitis. It is of possible significance that in this case an attack of chorea occurred six years before the epidemic encephalitis. Sometimes moderate polydipsia may be noted in infancy, the definite picture of diabetes insipidus appearing only as a sequel of a contagious disease (H. H. Turner), which should then be considered as an aggravating factor rather than as the cause.

Diabetes insipidus has been observed after measles. Findlayson reported such a condition in a boy 8 years of age, in whom diabetes insipidus was still present at the age of 16 years. There was polyuria, the daily output of urine being 12 to 15 liters. Angelini observed a hyperchloremic-hypochloruric type of diabetes insipidus which he attributed to a postmorbillic diencephalohypophysial lesion.

Diabetes insipidus may be a sequel of scarlet fever in children as young as 4 or 5 years of age (Külz). In the case of Blatt and Greengard the diabetes insipidus was of eight years' duration when the patient was examined at the age of 12 years. There was polyuria, the output being 8 to 14 liters; increased sugar tolerance was found; growth and development were retarded, and the child suffered from periodic attacks of vomiting and headaches. Solution of posterior pituitary double U. S. P. strength ("surgical pituitrin") administered hypodermically was effective.

Pertussis preceded a case of diabetes insipidus in which infantilism was also present (Gayler). Pertussis also played a role in H. H.

Turner's case, in which there was an accompanying adiposogenital dystrophy. Polyuria and polydipsia were somewhat improved in this case by the administration of solution of posterior pituitary ("pituitrin") as well as of "pitmelanin" and intermedin (extracts of the pars intermedia containing the chromatophorotropic principle). Daneri reported a case of encephalitis complicated by diabetes insipidus which followed pertussis in a boy 6 years of age. The child was drowsy and depressed; he had convulsions and there were psychic changes; the polyuria was as great as 14 liters. There was a favorable response to the administration of a posterior pituitary preparation.

In Whittle's case diabetes insipidus followed pharyngeal diphtheria, the symptoms subsiding spontaneously after three months.

Adiposity and diabetes insipidus as complications of mumps were reported by Flandin and his associates in a man 28 years of age. There was polyuria with daily excretion of 4 to 7 liters. The endocrine symptoms developed within a few weeks after the attack of mumps. It may be noted that in this case there was no involvement of the testicles during the attack.

Diabetes insipidus may complicate varicella, as in Salmi's case.

Of special interest is Roehm's case of postvaccinal encephalitis associated with diabetes insipidus. A boy 7½ years of age was vaccinated against smallpox. Seven days later he complained of headache and had fever, severe chills and an enormous thirst. He drank daily about 6.5 liters of water and voided 5.5 liters. He became difficult to manage and showed emotional instability. He reacted unfavorably to solution of posterior pituitary given hypodermically—suffering from chills and headache and doubling the intake and output of fluid—but received definite relief from barbital derivatives. Improvement in general health and disposition eventually occurred, but the diabetes insipidus improved very slowly.

Roentgenograms of the skull usually show normal conditions in these cases of encephalitic diabetes insipidus, and there are no definite changes in the eyegrounds. Diabetes insipidus may appear as a more or less striking sequel among postencephalitic symptoms such as insomnia, convulsions, tremor, acrocyanosis and parkinsonism. While moderate diabetes insipidus is sometimes found in this group,[26] the most extreme degrees of polydipsia and polyuria have also occurred. Whitehead and Darley reported the case of a boy 14 years of age whose output of urine amounted to as much as 30 liters or more a day. A great individual variability of intake and output has been noted for several patients of this type. Apparently polydipsia may be the primary and most important symptom; Snell and Rowntree mentioned a "compulsion type" of thirst.

26. Lesné and others, 1929; Mensi.

Extracts of the posterior lobe of the pituitary gland are frequently ineffective [27] against the postencephalitic types of diabetes insipidus. In certain cases they restrict the polyuria but do not affect the thirst; symptoms of water intoxication then become evident, nausea, vomiting and convulsions being serious manifestations.[28] Since the mentality of postencephalitic patients is frequently impaired,[29] they may continue their habit of drinking excessive amounts of fluid even when a posterior pituitary preparation is effective in diminishing urinary output. The administration of these drugs in such cases, therefore, should be accompanied by disciplinary measures in order to reduce somewhat the intake of fluid (Snell). In a case of postencephalitic diabetes insipidus reported by Signorelli, pituitrin was of little benefit, while spinal puncture proved effective. Lesné, Hutinel, Marquézy and Benoist, whose patient did not respond to solution of posterior pituitary given intranasally or by injection, reported good results with posterior pituitary powder applied intranasally.

*Summary.*—Typical symptoms of diabetes insipidus may follow encephalitis. When preceded by an acute contagious disease the diabetes presumably is caused by complicating encephalitis. Pitressin may have little effect in some of the cases. In patients with mental disturbance, symptoms of water intoxication may develop if pitressin diminishes the polyuria and excessive water drinking continues.

### DIABETES INSIPIDUS DUE TO TUBERCULOSIS

A tuberculous process at the base of the brain, involving either the pituitary gland or the diencephalon, may cause diabetes insipidus.

Before xanthomatosis was differentiated from tuberculosis the condition now termed the Hand-Schüller-Christian syndrome was mistakenly considered as tuberculous. Hand's important case, which belongs in this group, was not the first of this type to be reported. For example, the case described by Vámos before the publication of Hand's article can now be classified with the instances of the Hand-Schüller-Christian syndrome, although the author thought that the underlying process was tuberculous (see the section on xanthomatosis).

There are, however, reported cases in which tuberculosis must be accepted as the cause of diabetes insipidus. Healy described such a case, that of a boy 2½ years of age who had a daily urinary output of 6 liters. There was a trace of albumin in the urine. A diagnosis of tuberculous meningitis was made on the basis of the nervous symptoms. The roentgenograms of the skull showed nothing abnormal. The child's

27. Hall; Mensi.
28. Snell; Snell and Rowntree; Weir and others.
29. Hall; Whitehead and Darley.

mother had pulmonary tuberculosis. The patient's polyuria and polydipsia were controlled by a posterior pituitary preparation ("pituitrin"). The necropsy revealed miliary tuberculosis and external hydrocephalus; the basal cisternae were filled with a semisolid caseous exudate, and the pituitary gland was replaced by caseous tuberculous material. In von Hann's case the pituitary gland was also involved in a tuberculous process. The pituitary gland, however, is not always affected.[30] A special study of diabetes insipidus associated with tuberculous meningitis was made by Gold. There was no polydipsia in his cases, but moderate polyuria was present. In the cases reported by Hagenbach and by Haushalter and Lucien, tubercles were seen in the infundibular region at necropsy. Both of the patients cited by these authors were girls, 4 and 6 years of age. In both instances there was a history of tuberculosis in the family. The daily urinary output of Hagenbach's patient amounted to 10 liters, and that of the patient of Haushalter and Lucien, to 3 or 4 liters. In cases of diabetes insipidus associated with tuberculosis of the brain there may be expected such symptoms as anorexia, loss of weight, fever, drowsiness, stupor, rigor, rigidity of the pupils, twitching and convulsions. The tuberculin reaction, within its limitations, may be of value in differentiating this type of diabetes insipidus from other forms. The prognosis is obviously unfavorable.

*Summary.*—While tuberculosis of the brain may be accompanied by the symptoms of diabetes insipidus, this is not a cause of practical clinical importance. The prognosis is obviously bad, depending as it does on the underlying tuberculous involvement.

### DIABETES INSIPIDUS DUE TO SYPHILIS

Cases of diabetes insipidus due to acquired syphilis are usually easy to classify. In cases of diabetes insipidus in congenitally syphilitic children, however, it may be impossible to decide whether there is a causal relation between the two conditions or whether their coexistence is merely coincidental. The family described by Adolf Weil provides a good example (see the section on idiopathic hereditary diabetes insipidus). Obviously there was hereditary diabetes in this family, but only a few members of it were afflicted with syphilis. Under such circumstances it is clear that the two diseases had no causal connection. In other instances, however, particularly in those in which there is response of polyuria to antisyphilitic treatment but in which pitressin is not effective, the situation is confusing.

In diabetes insipidus due to acquired syphilis the underlying lesion may be a gumma in the diencephalopituitary region, basal meningitis or endarteritis (Nonne, 1915); in cases of congenital syphilis little is

30. Hagenbach; Haushalter and Lucien.

known about the pathologic changes underlying the diabetic condition, although a lesion in the diencephalopituitary region may be assumed. In fact, a calcified gumma was found in the hypophysis in Nonne's case (1915). Polyuria attributable to interstitial nephritis in patients with congenital syphilis was confused with diabetes insipidus only in the older literature.[31]

The intensity of the polyuria and polydipsia varies in the cases of diabetes insipidus attributed to congenital syphilis. Cases of mild involvement, with an output of 3 to 4 liters of urine, have been reported (Drouet and Hamel) as well as cases of a more severe condition with an output of 8 to 15 liters (Demme). The polyuria and polydipsia may occur at any age but are seldom present at birth; in some cases the symptoms were probably present as early as the age of 2 years but were not recognized with certainty until the age of 5 or 6 years; in others the onset occurred after puberty.[32] Associated symptoms noted in adults with acquired syphilis, such as polyphagia, sleeplessness, neuralgia, asthenia, vertigo and chilliness, are not regularly seen in children. In cases of diabetes insipidus based on congenital syphilis, both emaciation (Pacella) and obesity of the Fröhlich type [33] have been observed. Headaches, vomiting (Touraine, Golé and Bernou), profuse sweating, occipital pain, universal lymphadenitis (Demme), osteoperiostitis,[34] mental retardation and irritability [35] and epileptiform convulsions (Pashkoff and Smelov) have been reported. Encephalitic manifestations, such as general muscular rigidity, tremor and a masklike facial expression, may be accompanying symptoms (Dwyer). In Nonne's case a dense shadow was found in the region of the sella turcica.

The Wassermann reaction is usually strongly positive;[36] if not, the etiologic connection with syphilis is doubtful. The family history should be investigated carefully. Miscarriages, stillbirths or early deaths among the patient's relatives constitute evidence in favor of the diagnosis of congenital syphilis (Touraine, Golé and Bernou). The history of diabetes insipidus in nonsyphilitic members of the family suggests a coincidental occurrence of congenital syphilis and diabetes insipidus.[37]

The treatment consists primarily in antisyphilitic measures. In many cases these markedly improve the polyuria and polydipsia.[38] This was true of Dwyer's patient, although the encephalitic symptoms appeared

31. Versmann; Weber.
32. Bandler; Deebrey; Touraine and others.
33. Drouet and Hamel; Touraine and others.
34. Bandler; Catini; Demme.
35. Demme; Drouet and Hamel.
36. Catini; Pashkoff and Smelov; Touraine and others.
37. Pashkoff and Smelov; Adolf Weil.
38. Bandler; Catini; Demme; Pacella; Touraine and others.

to be intensified by the treatment. In some cases antisyphilitic treatment is not effective.[39] Improvement has been observed after the administration of extracts of the posterior lobe of the pituitary gland. It should be remembered that spontaneous improvement and remissions may occur in this type of diabetes insipidus (Demme).

*Summary.*—Diabetes insipidus may be caused both by congenital and by acquired syphilis. The presence of syphilis does not necessarily indicate a causal connection with diabetes insipidus. In cases of acquired syphilis lesions have been demonstrated in the diencephalopituitary region. The degree of symptoms of diabetes insipidus in syphilitic patients is variable. Treatment consists in antisyphilitic measures, which may or may not be successful, and in the administration of pitressin.

### DIABETES INSIPIDUS DUE TO XANTHOMATOSIS

Xanthomatosis, or lipoid granulomatosis, has only recently been recognized as a frequent cause of diabetes insipidus. In a review (Atkinson) of 103 cases of xanthomatosis in children diabetes insipidus was mentioned as a symptom in 61 instances, 58 of these cases having been described since 1920.

The basic lesion of the xanthomatous syndrome is a chronic noninfectious inflammatory granuloma,[40] which consists of foamy cells filled with lipoid substances. These cells, according to Rowland, are of reticuloendothelial origin. The xanthomatous or granulomatous cells replace the various normal tissues, thus causing a diversity of symptoms according to the location of the tumors. Although probably this process can involve any organ or tissue, a certain preference is manifest, and syndromes have been established according to the symptoms produced. This discussion will be limited to the syndromes of which diabetes insipidus is a symptom; the reader is referred to reviews [41] for a more complete study of the subject. The pathologic, xanthomatous changes causing the diabetes insipidus involve the hypophysis, which was seen to be affected in 13 necropsies (Atkinson). Of special importance is the fact that at necropsy xanthomatous changes of the pituitary gland could be demonstrated in some of these cases when the symptoms of polyuria and polydipsia had been present but exophthalmos and bony changes had been absent.

The best known xanthomatous syndrome is Hand-Schüller-Christian disease. In the case of a child with diabetes insipidus who also has exophthalmos and defective areas in the skull, the etiologic factor at the basis of this syndrome is readily recognizable. Sometimes the diag-

39. Levinson; Meijers; Rowntree, 1924.
40. Chester; Chester and Kugel.
41. Atkinson: Henschen: Rowland.

nosis is facilitated by additional symptoms which are more or less characteristic of xanthomatosis, such as xanthomas,[42] eczema of a maculopustular or seborrheic type,[43] hemorrhagic-purpuric lesions [40] and bronzing of the skin. Severe gingivitis and destruction of the alveolar processes are often present early in the disease and may cause loss of teeth. Sometimes there will be discovered protuberances of the skull corresponding to the areas of bony destruction. In certain cases roentgen examination of the pelvis, the long bones and the vertebrae reveals a destructive process corresponding to, though less characteristic than, that of the skull. Hypercholesteremia, if present, is a helpful diagnostic sign, although in some cases the blood cholesterol level is normal (Atkinson). Hepatosplenomegaly may be a finding, and generalized lymphadenitis is frequently present.

Some of the symptoms produced by the xanthomatosis are not particularly characteristic. To this group belong associated pituitary or diencephalic symptoms, such as dystrophia adiposogenitalis,[44] dwarfism,[45] Simmond's disease, hypogonadism (Chiari), mental deficiency (Kyrklund), otitis and deafness,[46] as well as neurologic manifestations of increased intracranial pressure [47] or focal neurologic symptoms. Headache, enlargement of the head, choked disks and such cranial nerve symptoms as facial paralysis and ptosis may readily lead to a diagnosis of tumor of the brain. In cases of xanthomatosis, phlyctenulas in the conjunctivas and pulmonary fibrosis may simulate tuberculosis.[48] Interesting changes of the fundi have been reported by Jaensch.

The polydipsia and polyuria caused by xanthomatosis are similar to those observed in other types of diabetes insipidus; sometimes they are only moderate in degree, but in other instances they are marked. One of Rowland's patients, who weighed only 10.5 Kg., excreted 6 to 8 liters of urine daily; Schüller's patient voided 7 to 9 liters. The basal metabolic rate has been found normal or moderately lowered (Atkinson).

As previously mentioned, the basic process in this type of diabetes insipidus will be recognized in the majority of cases by the associated symptoms of exophthalmos and bony lesions rather than by any peculiarity of the diabetic picture. However, if polyuria and polydipsia are the first symptoms to appear or if the other typical symptoms of xantho-

42. Egler; Futcher, 1901-1902; Griffith; Hand, 1893; Pusey and Johnstone; Schüller.

43. Cignolini; Comby; Henschen; Herzenberg; Merritt and Paige.

44. Kyrklund; Melli; Schüller.

45. Alberti; Grosh and Stifel; Kyrklund; Pusey and Johnstone; Schüller.

46. Atkinson; Grady and Stewart; Lichty; Sosman, 1930

47. Chester and Kugel; Chiari.

48. Henschen; Jaensch; Rietschel; Rowland.

matosis fail to develop, the condition might easily be classified as idiopathic diabetes insipidus. Henschen cited the cases of 5 children who had diabetes insipidus and bony lesions but not exophthalmos. He also mentioned reports of 5 children who had diabetes insipidus probably caused by xanthomatosis but who manifested none of the other cardinal symptoms of the Hand-Schüller-Christian syndrome.

Xanthomatosis may occur at any age but appears to be more frequent in childhood. It may show symptoms even in infancy. For example, in a case described by Horsfall and Smith the symptoms of polydipsia and polyuria dated from the age of 3 months, necropsy subsequently demonstrating that the underlying process was xanthomatosis. Males are affected in the ratio of 2 to 1 female. There is no racial preference. Infection, measles in particular, and trauma are often mentioned in the literature as inciting factors.

The course of this form of diabetes insipidus varies. It was formerly thought that the outcome was always unfavorable. This is not true, however, and it now seems certain that some of the patients recover, sometimes without any particular treatment (Tate).

Extracts of the posterior lobe of the pituitary gland are often beneficial in the symptomatic treatment of this form of diabetes insipidus. In some cases the dose must be increased from time to time, and the extracts may eventually become ineffective.[49] Two other methods of treatment have been suggested: a fat-free diet, in the attempt to reduce the blood cholesterol to a normal level (Bürger), and roentgenotherapy of the pituitary region.[50]

*Summary.*—Xanthomatosis is a frequent cause of diabetes insipidus, which in this case usually constitutes part of the Hand-Schüller-Christian syndrome. Polyuria and polydipsia may appear as the first symptoms in this complex or when other manifestations of it are not characteristic. Xanthomatous diabetes insipidus occurs more frequently in children than in adults and may even occur in infants. Arrest or spontaneous remission in the symptoms may take place. Treatment consists of the administration of pitressin and a fat-free diet and roentgenotherapy of the hypophysial region.

### DIABETES INSIPIDUS DUE TO TUMORS OF THE BRAIN

Diabetes insipidus has been observed as a symptom of tumors of the brain of various histologic types and of different origins. The disturbance is caused either directly, by destruction or replacement of the diencephalopituitary system by the tumor, or indirectly, by pressure of the

49. Denzer; Horsfall and Smith; Lesné and others, 1932; Rowland.
50. Cignolini; Melli; Sosman, 1930; Sparrow and Fetner.

new growth on this region. If a tumor prevents the passage of fluid between the ventricles, internal hydrocephalus may be the responsible factor.

Sometimes diabetes insipidus is an early manifestation of a tumor of the brain; it may precede pressure symptoms by years. In cases of this type the disease is often at first diagnosed as idiopathic diabetes insipidus. Occasionally, careful, repeated examinations of the eye-grounds and the skull may result in discovery of the neoplasm before the appearance of marked pressure symptoms. In cases of tumor of the diencephalopituitary region diabetes insipidus is frequently accompanied by other symptoms of endocrine disturbance. Polyuria and polydipsia have been observed as early symptoms of tumor of the brain in children 3 or 4 years of age.[51] How soon other symptoms of tumor will follow cannot be predicted. Long intervals have frequently been observed. In Nonne's case (Leschke) diabetes insipidus was present in a child 3 years old; nineteen years later the patient died after callosal puncture, and a glioma of the base of the pons, compressing the diencephalon, was found. Rosenbloom reported a case in which symptoms of diabetes insipidus were present in a girl of 3½ years, but she was 12 years old before generalized symptoms of tumor revealed the underlying cause of the condition. In these cases slowly growing gliomas or suprasellar cysts usually explain the gradual development of the symptoms, but cases of carcinoma (Wentzler) and sarcoma (Simmonds) of the diencephalo-pituitary region have also been reported in which diabetes insipidus or retardation of growth has preceded death by as many as five years. One of our patients (case 1) had no definite symptoms of tumor until two years after the onset of diabetes insipidus. Occasionally the polyuria and polydipsia disappear a short time before death[52]; they may disappear also after operation (Moffett). Occasionally they are increased after decompression (Cushing, 1912 and 1932).

The intensity of the polyuria and polydipsia in cases of tumor varies. Usually, as was true of 1 of our patients (case 1), from 2 to 4 liters of urine is excreted daily. However, it has been reported that in several cases of tumor involving the base of the brain there was excretion of 8 to 11 liters[53] and in cases of pineal tumor of as much as 20 to 24 liters (von Hoesslin). In the majority of cases reduction of thirst and of urinary output followed the administration of posterior pituitary solution or powder.[54]

51. Martin and Cushing; Moffett.

52. von Hoesslin; Martin and Cushing; Wentzler.

53. Moffett and Greenberger; Römer.

54. Moffett and Greenberger; Römer; Rosenbloom.

Infantilism (Wentzler) and sexual underdevelopment [55] have been reported most frequently as the accompanying endocrine symptoms. Obesity of various degrees [56] has been observed in many cases; this may be followed by emaciation when symptoms of pressure appear (Doyle and Kernohan). Precocious sexual development may accompany diabetes insipidus due to hydrocephalus or tumor of the brain (case 2).

Among frequently observed associated symptoms are frontal [57] and supraorbital (Wentzler) headache, which appear early, and dizziness. Less often described are nausea and vomiting (usually occurring in the advanced stage only), tremor (Globus), staggering gait (Jewett), exaggerated reflexes,[58] disturbance of temperature regulation, which may lead to fever (Martin and Cushing) or subnormal temperature,[59] and enlargement of the head.

Among accompanying ocular disturbances are progressive loss of vision, temporal and homonymous hemianopia (Doyle and Kernohan), constriction of the visual fields for form [55] and double vision (Horrax and Bailey). Examination of the fundi reveals atrophy of the optic nerve in the majority of the cases [60] and sometimes a superimposed choked disk.[61] In rare cases the fundi may be normal even in the advanced stages (Horrax and Bailey). Ptosis (Horrax and Bailey), strabismus and nystagmus have occasionally been noticed.[62] The pupils are frequently unequal and do not react to light.[63]

The mentality of patients with tumors has often been described as dull;[64] on the other hand, irritability may be manifest. In the terminal stage drowsiness and somnolence [65] are frequently present. Sudden variation in the symptoms may sometimes suggest hysteria.

In a number of cases the sella turcica was found to be normal and the roentgen examination of the skull gave entirely negative results; in others the sella turcica was enlarged (Cushing, 1912 and 1932) or calcareous masses were visible above [66] or behind it (Moffett and Green-

55. Cushing, 1912 and 1932; Jewett.

56. Bartels; Cushing, 1912 and 1932; Doyle and Kernohan; Laffon; Martin and Cushing.

57. Doyle and Kernohan; Horrax and Bailey; Jewett.

58. Cushing, 1912 and 1932; Moffett and Greenberger.

59. Bartels; Horrax and Bailey; Jewett.

60. Bartels; Cushing, 1912 and 1932; Martin and Cushing; Moffett; Moffett and Greenberger.

61. Bartels; Cushing, 1912 and 1932; Newmark.

62. Cushing, 1912 and 1932; Martin and Cushing.

63. Cushing, 1912 and 1932; Horrax and Bailey.

64. Cushing, 1912 and 1932; Martin and Cushing; Römer.

65. Jewett; Moffett.

66. Laffon; Moffett.

berger). Increased convolutional markings may be present. Separation of the sutures is seen in children if the intracranial pressure is markedly increased from obstruction of the flow of the cerebrospinal fluid.

Marked asthenia (Cushing, 1912 and 1932), convulsions (Jewett) and profuse perspiration (Doyle and Kernohan) have been mentioned as symptoms occurring in the advanced stage.

A variety of tumors may lead to diabetes insipidus, and clinical differentiation is usually impossible. Even exploratory operation sometimes fails to determine the type of tumor present.

Chiasmal gliomas are accompanied by diabetes insipidus in about one fourth of the cases. These are suprasellar tumors which may be confused with pituitary neoplasms or with those of the pharyngeal pouch. In a case (Martin and Cushing) of glioma in a boy 2 years of age there was polydipsia. The child had fallen down stairs about six months previously. The mental development was retarded, and he did not learn to talk, but he was overdeveloped in size and weight. Progressive loss of vision and bilateral atrophy of the optic nerve were present. The physical overdevelopment was interpreted as a pineal reaction, and a pineal tumor was suspected. Callosal puncture was performed. Approximately ten months later, when the child died, a glioma of the chiasma with invasion of the optic nerve was found at necropsy. In a case of tumor in a girl 13 years of age reported by Cushing (1932), oculomotor palsy and blindness of the right eye were present. A history of preceding polyuria and polydipsia was obtained, although polyuria had ceased at the time of the examination. It was ascertained that the girl had begun to grow stout a few months before the ocular symptoms developed. Mental deterioration followed. Hyperpyrexia was noted, the physical examination revealed primary atrophy of the optic nerve, and the roentgenograms showed a normal sella turcica without suprasellar calcification. An exploratory operation revealed a chiasmal tumor extending into the third ventricle.

A teratoma of the base of the diencephalon caused polyuria in a girl 16 years of age reported on by Cushing (1912). She had not menstruated, and her development was infantile. She suffered from headaches and vomiting. Shrinkage of the visual fields for form but without hemianopia was present. Exaggerated reflexes were found. Three exploratory operations were futile, and necropsy revealed a teratoma containing cartilage, bone cells and myxomatous tissue. A teratoma caused diabetes insipidus, fatigue, irritability, ptosis, facial weakness and weakness of the legs in a girl of 6 years; this child also showed marked hypertrichosis (Globus).

Sarcoma of the base of the brain caused polyuria, extreme thirst and emaciation in a boy 9 years of age who had been physically retarded for the preceding five years (Simmonds). Necropsy revealed a hemor-

rhagic sarcoma bulging into the third ventricle and metastases in the neurohypophysis as well as in the pituitary stalk.

A ganglioneuroblastoma in the third ventricle with destruction of the tuber cinereum and corpora mamillaria and invasion of the optic tract caused diabetes insipidus and obesity in a girl aged 10½ years (Doyle and Kernohan). At the age of 13 years these symptoms disappeared, but progressive loss of vision, frontal headaches on the right, vomiting, profuse perspiration and general weakness indicated that the pathologic process had advanced. There was a difference between the size of the pupils, but they reacted to light. The optic disks were full and pale.

Craniopharyngeal cysts are derived either from Rathke's pouch or from the hypophysial duct. A cyst of Rathke's pouch was found in a girl aged 3½ years who had suffered from polyuria, polydipsia and supraorbital headaches (Moffett). She lost weight and became apathetic and drowsy; atrophy of the optic nerve was discovered, and roentgen examination showed enlargement of the sella turcica and calcareous masses extending backward from the posterior clinoid process. After operation the diabetes insipidus disappeared, but the atrophy of the optic nerve persisted.

Carcinoma of the posterior lobe of the pituitary gland and of the tuber cinereum was found in the case of a boy who manifested diabetes insipidus in his fifth year (Wentzler). At that time the sella turcica and the eyegrounds were found to be normal. The child's paternal grandmother was said to have suffered from great thirst. "Pituigan powder" and other preparations of the posterior lobe of the pituitary gland applied intranasally had no effect. It was therefore concluded that the child was a dipsomaniac. However, he became emaciated, and his growth was retarded. The intake and output of fluid were between 3 and 4 liters per day. The specific gravity of the urine was about 1.002, but concentration to 1.014 was possible. Fever, loss of weight and apathy indicated that an organic disturbance was present. For a short period during treatment with insulin there was an increase of weight. The output of urine decreased to 1,600 cc. after the insulin therapy was stopped. The child died suddenly. Necropsy revealed a large cell carcinoma of the posterior lobe of the pituitary gland and the tuber cinereum. The anterior pituitary lobe, the kidneys, the pancreas and the other organs were normal.

In 1 reported case (Newmark) an infundibular tumor, probably of epithelial character, extending forward between the frontal lobes and backward into the third ventricle, destroyed the neurohypophysis and most of the pars intermedia. Severe polyuria and polydipsia had existed for five years, but general symptoms of tumor, such as vomiting, bradycardia, papillitis, anosmia, delirium and ankle clonus, appeared only two weeks before the patient's death, at the age of 14 years. On

roentgen examination the sella turcica appeared normal. Of interest was the high tolerance to alcohol manifested by this patient.

An interpeduncular tumor [67] reaching the stalk or the posterior portion of the pituitary gland may cause diabetes insipidus. If such a tumor is of slow growth, it also causes infantilism and sometimes obesity. As the process advances there may be headache, vomiting, failing vision, strabismus, inequality of the pupils, tremor, convulsions, enlargement of the sella turcica, atrophy of the optic nerve or choked disk.

An embryoma of the pineal gland in a boy of 8 years has been reported as the cause of diabetes insipidus (Hijmans van den Bergh and van Hasselt). Precocious development of the secondary sexual characteristics made the clinical diagnosis possible. Sarcoma of the pineal gland has been reported in a boy of 9 years with a high degree of polyuria (von Hoesslin). Pinealomas were associated with diabetes insipidus in 2 interesting cases reported by Horrax and Bailey. In 1 case a pinealoma and a chiasmal glioma were seen at necropsy in a boy 13 years of age. In the other case there was association of a vascular tumor of the third ventricle with a small pinealoma. Which tumor caused the diabetes insipidus cannot be decided, but it is probable that the pinealoma was of minor importance in this respect. One of our patients (case 2) probably had a pinealoma.

*Summary.*—Diabetes insipidus may be caused by different types of brain tumor, the mechanism being pathologic changes in the diencephalopituitary region. Polyuria and polydipsia may precede endocrine and pressure symptoms by several years and may be moderate or severe. The accompanying endocrine symptoms are multiform and are those commonly associated with pituitary and pineal dysfunction.

## RARE CAUSES OF DIABETES INSIPIDUS

Diabetes insipidus may occur in cases of leukemia. Lenk reported a case of acute myeloblastic leukemia in a young man 20 years of age. This patient was apparently well until two and a half months before his death, although it was remarked that his beard and his pubic and axillary hair had not developed. The first symptoms were frontal headaches without vomiting and, six weeks later, polyuria and polydipsia. The output of urine amounted to about 8½ liters, the specific gravity being as low as 1.001. Generalized lymphadenitis, pallor, epistaxis and a palpable spleen directed attention to the hemopoietic system. The erythrocyte count was 2,249,000; the leukocyte count varied from 34,500 to 82,000. There were 81 per cent myeloblasts. The eyegrounds were normal. The temperature ranged from 100 to 104 F. At necropsy a persistent thymus and a hypoplastic aorta were noted;

67. Cushing, 1912 and 1932; Jewett; Römer.

results of the histologic examination of the brain were negative, but the pituitary gland was not examined. Sheldon reported lymphatic leukemia of the aleukemic type causing diabetes insipidus in a man 20 years of age who had had lymphadenitis for at least two years. Five months before his death a membranous exudate and also an exanthem consisting of firm pink circular plaques appeared on the tonsils. The erythrocyte count was 4,820,000; the leukocyte count was 7,680, with 63 per cent polymorphonuclears, 30 per cent lymphocytes, 3 per cent mononuclears and 1 per cent basophils. Moderate diabetes insipidus with a urinary output of 4.5 liters was observed two weeks before death. At first the administration of a posterior pituitary preparation ("pituitrin") relieved the condition, but later this was ineffective. At necropsy a diffuse lymphocytic infiltration of the pituitary gland was observed.

Diabetes insipidus caused by malignant lymphogranulomatosis (Hodgkin's disease) was reported by Desbuquois, who attributed this symptom to a probable metastatic tumor of the infundibulum. The urinary output was 14 to 15 liters. There were symptoms of intracranial hypertension, and spinal puncture reduced the excretion to 5 liters. The sella turcica and the eyegrounds were normal, but there was impairment of the visual fields. Glycosuria was found to be associated with the diabetes insipidus. Treatment with insulin and a posterior pituitary preparation relieved both types of diabetes.

Diabetes insipidus was reported as a symptom of Schaumann-Besnier-Boeck disease in a boy 10 years of age by Lesné, Launay and Sée and in an adult by Tillgren. This condition consists in the formation of sarcoids, frequently localized in the skin of the face (lupus pernio) or in the fingers: If it is in the latter there is involvement of the bones and the periarticular regions, and the mistaken diagnosis of spina ventosa may be made. The sarcoids may be present in other organs, such as the lungs, and probably also in the diencephalopituitary region when diabetes insipidus is a symptom. Tillgren examined the lesions and found epithelioid foci without necrosis and giant cells of the Langhans type enclosing chromatophilic bodies with a concentric structure. He considered the process benign lymphogranulomatosis. In the case reported by Lesné, Launay and Sée pseudo spina ventosa had appeared two years before the diabetes insipidus. The polyuria was of moderate degree (3 to 4 liters) and had been present for two years at the time of observation. It responded to nasal applications of posterior pituitary powder. Mild obesity accompanied the diabetic condition. The patient's intelligence was good. Roentgenograms of the digits revealed cystic formation.

Belkowski reported diabetes insipidus as a symptom of actinomycosis in a boy 19 years of age. The urinary output amounted to about 8

liters daily. Headache and pain in the neck, ear and cervical part of the spine were the chief complaints. The reflexes were increased; there was nystagmus, and present also were changing palsies of the muscles of the face and extremities. A tumor developed on the left side of the neck; on puncture it yielded pus containing actinomycetes. Necropsy revealed internal hydrocephalus and thickening of the dura in the region of the sella turcica.

Internal hydrocephalus of undetermined origin caused diabetes insipidus in a case reported by Strauch. A girl about 8½ years of age had shown symptoms of diabetes insipidus for several months. She had a ravenous appetite; she was obese, and pubic hair was present. The Wassermann reaction was negative. Late in the course of the disease bilateral optic neuritis was discovered. A shallow sella turcica, reduction of the clinoid processes and open sutures were seen in the roentgenograms. Supraorbital headaches, dizziness, vomiting, generalized weakness, ataxia, enlargement of the head, slight exophthalmos, bulging of the veins of the eyelids, increased reflexes and ankle conus were present. While the diagnosis of tumor of the brain appeared justified from the symptoms, only hydrocephalus of unknown origin was seen at necropsy.

Diabetes insipidus occurring in the course of a deficiency disease is of particular interest. Rassulev estimated that 25 per cent of patients with pellagra present symptoms of diabetes insipidus. Although in the majority of cases the polyuria is mild, an excretion of from 4 to 7 liters has been observed. The specific gravity of the urine is low, and restriction of fluid does not lead to better concentration. Spontaneous changes are noted in the course of the disease. According to Rassulev a normochloremic and hypochloruric type of diabetes is found with pellagra. A red, glazed tongue, cutaneous lesions on the exposed parts of the body, bradycardia, emaciation, enterocolitis, intellectual decline, irritability, "neurasthenia" and sleeplessness may be seen as associated symptoms of the pellagrous condition. Since some of these signs also occur with other forms of diabetes insipidus, it is easily understood why in isolated cases of pellagra this condition may not be recognized. The symptoms of polyuria and polydipsia appear several weeks or months after the onset of the pellagra and therefore in an advanced stage of the disease, a fact which connotes a serious prognosis. If the symptoms of pellagra improve, the signs of diabetes insipidus disappear gradually. The treatment consists of that for pellagra, namely, a high caloric diet and the oral administration of about 250 Gm. of brewers' yeast daily; nicotinic acid may also be given.

A possible relation of the thyroid gland to diabetes insipidus must be considered in certain cases.[68]

68. McConnell; Strauss.

*Summary.*—Diabetes insipidus may rarely accompany a number of conditions, such as leukemia, lymphogranulomatosis, Schaumann-Besnier-Boeck disease and actinomycosis. The mechanism is infiltration of the diencephalopituitary region by the specific pathologic process of the disease. Diabetes insipidus may also be a symptom in advanced stages of pellagra.

## SYMPTOMATOLOGY

Polydipsia and polyuria are the outstanding symptoms of diabetes insipidus. According to the accepted theories of diabetes insipidus, polyuria should initiate the vicious circle and should be followed necessarily by polydipsia. Several cases, however, have been described in which the thirst has preceded the polyuria by several hours.[69] The most convincing evidence on this point consists in the description of the sudden onset of diabetes insipidus after trauma and certain experimental data presented by Bailey and Bremer, who noticed after injury of the hypothalmus in dogs an increased intake of water one day before the onset of polyuria. In deciding this question, the differentiation between polyuria and micturition should be kept in mind. That is to say, an increase in the volume of urine may precede micturition by several hours, particularly in a person who has just suffered a severe trauma, who has not been completely conscious and who, therefore, may not void.

In the case of an infant with diabetes insipidus, polydipsia is usually the first symptom to attract the mother's attention. When fed at the usual intervals he is not satisfied but becomes restless and cries as soon as he is removed from the breast or his bottle feeding is over. If his thirst is mistaken for hunger, he may be given additional food. Eventually there occur the results of chronic overfeeding, and diarrhea may develop (Liebmann). Polyuria is often not marked in cases of infantile diabetes insipidus, since in early as compared with later life the exchange of water is regulated to a greater extent by the gastroenteric tract and the skin than by the kidneys (Veil, 1923). In infants, therefore, diabetes insipidus is not easily recognized except in families in which the disease occurs frequently (Adolf Weil). In older children, however, the polyuria is sometimes so striking that it cannot be overlooked. Children 5 or 6 years of age sometimes void 400 to 500 cc. at one micturition. Enlargement of the bladder occurs with chronic involvement. A boy weighing 13 Kg. voided 9 to 15 liters of urine daily (Vierordt); another, 16 years of age, was said to have excreted 35 liters daily, his bladder having a capacity of 1,850 cc. (Rowntree, 1924). An excretion of 43 liters in twenty-four hours has been reported for an adult (Trousseau). Mild polyuria may have a more serious prognosis than marked

69. Allen and Sherrill; Leschke; Rowntree; Weir and others.

involvement, the factor of significance being the underlying pathologic process and no clue being furnished to this by the amount of urine voided. Sometimes the output of urine temporarily exceeds the intake of fluid, the excess being derived either from the food ingested or from the body tissues. When observations are continued over a long period, however, the fluid intake and output are in balance (Futcher, 1901-1902).

Children with diabetes insipidus void frequently at night; they either get up many times or wet the bed. When proper toilet habits have already been established, the enuresis is often the first symptom to attract attention. Although statistically diabetes insipidus as a cause of enuresis is rare, it should be considered in every case.

With chronic involvement the intensity of the polyuria undergoes variations which cannot always be satisfactorily explained. In case of diabetes insipidus caused by a tumor, the disappearance of the polyuria and polydipsia often indicates the last stage of the disease. This occurred in 1 of our patients (case 1). Many authors[70] have reported that the symptoms of diabetes insipidus disappear during febrile periods. The fact that the kidney regains its ability to concentrate under abnormal conditions is of great interest and must be taken into consideration in all theories that attempt to explain the physiologic mechanism of diabetes insipidus. Improvement of the polyuria and polydipsia during pregnancy is the exception; in most cases of chronic idiopathic diabetes insipidus an increase in the symptoms at such a time has been reported (Adolf Weil). Improvement of symptoms during puberty is sometimes observed,[71] a fact which has led to attempts to cure diabetes insipidus by the administration of extracts containing "sex hormones" (see the section on treatment). Sexual activity sometimes has a beneficial effect on the symptoms in the idiopathic-hereditary type (Adolf Weil). Exercise increases thirst and, subsequently, polyuria; rest has a beneficial influence. Thus the symptoms of mild involvement may disappear after admission to a hospital because the child is kept in bed. Sometimes, too, patients who do well in the hospital under treatment with a certain dose of a posterior pituitary preparation relapse at home, although the treatment is continued.

In cases of diabetes insipidus the urine is pale or colorless. The specific gravity is 1.001 to 1.005. The total daily excretion of solids is approximately normal. Traces of albumin and inosite are sometimes found. The amount of chloride varies but is always lower in the urine than in the blood plasma (see the section on pathologic physiology). Urea, though more concentrated than in the plasma, is much diluted in

70. Forschbach and Weber; Grote; Leschke; Strubell; Veil, 1923; Adolf Weil.
71. Marañon; Silvestri.

comparison with the normal concentration in urine, and this is true also of the other normal urinary constituents.

Results of phenolsulfonphthalein and urea clearance tests have been found to be within normal limits. After administration of solution of posterior pituitary ("obstetrical pituitrin") to a patient with diabetes insipidus, the kidney is able to excrete a larger amount of phenolsulfonphthalein than before (Hachen).

Thirst, which is probably merely a secondary manifestation,[72] is the outstanding subjective symptom. With severe involvement it tortures the child day and night and disturbs his rest as well as that of his parents. It makes regular attendance at school difficult and interferes with the child's normal development by restricting his activities. A trip on the street car or a short hike becomes a problem. Secondary psychic changes become inevitable in the more serious conditions. Some children, however, drink with great pleasure and are happy as long as their intake of fluid is not restricted. In isolated cases the quenching of the thirst is not limited to the drinking of water. Newmark described the case of a boy who preferred beer and who consumed as much as 4 liters of this beverage within a short time. This patient did not feel any stimulating or intoxicating effects from his drinking bouts. As a matter of fact, resistance to alcoholic intoxication has been observed repeatedly in patients suffering from diabetes insipidus (Trousseau). Dryness of the mucous membranes of the mouth and decreased secretion of saliva remind the child constantly of his condition. One patient, whose diabetes insipidus was accompanied by symptoms of tumor of the brain, located his thirst definitely in the interior of his nose (Christie and Stewart).

Marked restriction of fluids for patients with diabetes insipidus may lead to collapse. Headache, fatigue, muscular pain, hypothermia, rapid loss of weight and tachycardia are premonitory symptoms. This collapse may be accompanied by severe psychic disturbances which are not easily distinguished from the furor and delirium manifested by children with primary polydipsia whose fluid intake has been limited (Beumer). Primary polydipsia is not rare in psychotic children, and its differentiation from true diabetes insipidus is impossible as long as the patients are allowed to drink freely. The urine of patients with primary polydipsia both qualitatively and quantitatively resembles that of children suffering from diabetes insipidus. The differentiation is rendered still more difficult because psychic disturbances are also encountered in children with diabetes insipidus. Then, too, the changeable symptoms seen when the disease is caused by a slowly growing tumor may be mistaken for psychopathic manifestations. It is not surprising that a child who

72. Finkelnburg, 1907; Richter, 1935; Richter and Eckert.

is tortured day and night by polyuria and polydipsia becomes "neurasthenic." Therefore, diabetes insipidus and primary polydipsia can be definitely differentiated only if the experiment of withholding fluid is successfully performed (see the section on diagnosis).

So long as the child with diabetes insipidus is permitted to drink freely, the hemoglobin and the blood cells remain unchanged, except when the condition is symptomatic and the underlying process influences them. The blood volume is within normal limits (Rowntree, 1924). The composition of the plasma is usually unchanged, although relative or absolute hemodilution has been reported as well as hemoconcentration (Peters). Quantitatively the serum proteins are usually within normal limits. It has been claimed that their colloid-osmotic pressure is increased (Baráth and Weiner). The nonprotein nitrogen and the sugar content are normal. The chloride content is sometimes high; in rare cases, low. This variation has been made the basis of a classification of diabetes insipidus into hyperchloremic and hypochloremic types (see the section on pathologic physiology).

The symptoms so far discussed do not complete the clinical picture usually encountered in cases of diabetes insipidus. The remainder of the pathologic signs, however, do not, strictly speaking, pertain to the symptomatology of diabetes insipidus but are associated symptoms, which will be discussed in the section on diagnosis.

*Summary.*—The important symptoms of diabetes insipidus are polydipsia and polyuria, the degree of these varying considerably in different patients and also from time to time in the individual patient. Exercise tends to increase polydipsia and therefore polyuria, and rest, to decrease both. In early life the polydipsia of diabetes insipidus may be confused with hunger because of the amount of feeding demanded. In infants polyuria may not be marked because of regulation of water exchange by the gastroenteric tract. The degree of polyuria is not related to prognosis, this depending rather on the underlying pathologic factor responsible for the diabetes. The urine is pale, its specific gravity low, its chloride content lower than that of the blood plasma and its urea content reduced. Functional kidney tests usually give results within normal limits. The blood shows normal values for hemoglobin and cells (unless the underlying cause influences them); the volume, plasma and proteins of the blood are usually normal quantitatively, and the two last, also qualitatively; there may be increase or decrease of blood chlorides. Marked restriction of fluid intake causes water intoxication with such symptoms as headache, fatigue, loss of weight, hypothermia, tachycardia and finally collapse. True diabetes insipidus must be differentiated from primary polydipsia, the latter resembling diabetes insipidus symptomatically but showing, on restriction of water, prompt diminution in the amount of urine and increase in its specific gravity.

## DIAGNOSIS

The diagnosis of diabetes insipidus is made easy by its cardinal symptoms of polydipsia and polyuria, but it should be determined, if possible, whether some underlying pathologic process is responsible or whether the condition must be classified as idiopathic (Rowntree, 1921).

Temporary polyuria may occur under a variety of conditions, as during exposure to cold, with nervous excitement, after the ingestion of large amounts of fluid and after defervescence in febrile disease. These conditions may be differentiated from diabetes insipidus without difficulty. On the contrary, primary polydipsia, a symptom occurring in psychotic patients, is not so easy to distinguish from true diabetes insipidus,[73] since the essential symptoms are identical in the two conditions. When a concentration test is performed, however, primary polydipsia can be recognized by the prompt reduction of the urinary output and a simultaneous increase in the specific gravity to from 1.020 to 1.030. In diabetes insipidus, under identical conditions, the amount of urine will continue to be greater than normal; the specific gravity as a rule will not exceed 1.005 to 1.007, and the loss of fluid will be reflected in a rapid loss of weight. Psychotic patients in whom primary polydipsia is a symptom may not be sufficiently cooperative to assist in the concentration test or may resort to ruse in order to obtain fluid. The presence of psychopathic symptoms, however, is of little assistance in the differential diagnosis, since patients with diabetes insipidus are often mentally disturbed or hysterical when deprived of fluid.

Diabetes mellitus can be differentiated from diabetes insipidus in most cases by urinalysis or by determining the fasting level of the blood sugar or the dextrose tolerance. Occasionally diabetes insipidus changes finally to diabetes mellitus (Senator), or the two conditions may be combined.

Moderate polyuria is sometimes encountered with acute infections of the urinary tract (de Lange, 1933), in which case white or red blood cells or bacteria will be found in the urine.

In cases of moderate polyuria and polydipsia chronic nephritis must be ruled out (Chown and Lee). In cases of diabetes insipidus there is usually no albuminuria; and the nonprotein nitrogenous constituents of the blood, the elimination of phenolsulfonphthalein and the blood urea clearance are within normal limits. Diabetes insipidus, of course, can occur in a nephritic patient.

The symptoms of polycystic kidneys, when renal insufficiency becomes manifest, include polyuria and polydipsia. In case of congenital deformities of the urinary tract complicated by secondary infections, the polyuria

73. Achard and Ramond; Bauer; Ebstein; Labbé and others, 1931; Reichardt.

and polydipsia present are sometimes designated as pseudo diabetes insipidus (de Lange, 1933).

Since the treatment of diabetes insipidus depends on the nature of the basic process, it is important to discover any underlying pathologic changes. It is obvious that little information can be gained from an analysis of the degree of polyuria and polydipsia, since these present no distinguishing characteristics with the different pathologic conditions or with the idiopathic form of diabetes insipidus. Information of value may be secured by investigation of the family history, the past history of the patient and the associated symptoms.

The familial occurrence of diabetes insipidus indicates that the case under observation may belong to the idiopathic-hereditary group. If the mother has aborted or miscarried before the patient's birth, congenital syphilis must be considered. Tuberculosis in the child's environment suggests the possibility that a tuberculous process is the basis of the diabetes insipidus. Knowledge of the past history aids in classifying postencephalitic and postinfectious types. Sometimes a history of trauma to the head reveals the cause of the diabetic condition, although it may, of course, only be misleading.

The patient's age is of diagnostic significance. The congenital type usually is hereditary; xanthomatosis is frequent in early childhood, while as a rule tumors and postencephalitic processes are encountered in later childhood.

The child's general health and the associated symptoms may be important in differential diagnosis. Diabetes insipidus in an otherwise healthy child usually belongs in the hereditary group. In early stages of tumor or xanthomatosis there may be few symptoms other than the diabetes, while the same processes in their advanced stages may present a picture of severe prostration and asthenia. Miliary tuberculosis and tuberculous meningitis as the cause of diabetes insipidus are not difficult to diagnose, provided they are sufficiently advanced. Hydrocephalus can also be readily recognized, and the same is usually true of postencephalitic syndromes. In the majority of instances, however, the symptoms of the causative pathologic condition are not characteristic, and a thorough investigation of the associated symptoms is necessary.

Increased or subnormal body temperature may accompany several pathologic processes, so that little diagnostic aid can be derived from this symptom. Elevation of temperature may be due to an inflammatory process or to local involvement or disturbance of the center which regulates temperature, presumably located in the hypothalmic region. Subnormal temperatures, so frequently noted when the disease is severe, may be due to loss of heat after ingestion of large quantities of water (Rowntree, 1924) or to disturbance in the nervous centers.

The general nutritional status is normal in many cases. Some children with diabetes insipidus may be obese, the cause being syphilis, xanthomatosis, tumor, idiopathic hydrocephalus or a post-traumatic or postinfectious lesion. If diabetes insipidus is present in a case of the Laurence-Moon-Biedl syndrome, obesity will also be present. Loss of weight has been noted in many cases and is to be expected with tuberculosis, the late stages of brain tumor, pellagra and xanthomatosis. When the pathologic process has destroyed the pituitary gland completely, Simmond's disease results.

Hypogenitalism may occur in cases of diabetes insipidus due to tumor of the brain, trauma, infectious disease or xanthomatosis; it has also been observed in 1 case in which the cause was supposedly leukemia.

Sexual precocity and diabetes insipidus occur simultaneously in cases of tumor of the pineal gland, and this combination of symptoms in cases of "idiopathic" hydrocephalus (Strauch) has been reported.

Retardation of growth or dwarfism may accompany diabetes insipidus in cases of tumor, xanthomatosis or postencephalitic involvement. Acromegaly does not, of course, occur in children but was observed in a congenitally syphilitic patient in the third decade of life who also had diabetes insipidus.

Generalized lymphadenitis is present in cases of leukemia, syphilis and xanthomatosis. Purulent cervical adenitis has been noted with actinomycosis.

There may be the residual symptoms of a previous trauma of the head. Tumorlike elevations of the skull occur in cases of xanthomatosis; roentgenograms will reveal the membranous nature of the portions of the skull beneath the tumors. Enlargement of the head may be due to tumor or to "idiopathic" hydrocephalus.

If a harelip or a cleft palate is present, the diabetes insipidus may be due to a developmental abnormality.

A smooth, glazed, highly red tongue suggests pellagra. Gingivitis, sore mouth and loss of teeth are frequent and early symptoms of xanthomatosis. Atypical membranes on the tonsils are associated with leukemia.

In cases of tuberculosis there may be more or less typical signs in the lungs. Roentgenograms of pulmonary tuberculosis must be differentiated from somewhat similar pictures sometimes seen in cases of xanthomatosis. Enlargement of the structures in the mediastinum may aid in the diagnosis of leukemia accompanied by diabetes insipidus. Shadows produced by sarcoids in cases of Schaumann-Besnier-Boeck disease may sometimes be seen in roentgenograms of the lungs.

With diabetes insipidus there are no characteristic changes in the heart. In spite of the enormous amount of fluid transported by it,

enlargement, or hypertrophy, practically never occurs, since the volume of blood is not increased. The presence of cardiac hypertrophy and polyuria may indicate, with other signs, that the patient is suffering from renal insufficiency rather than from true diabetes insipidus. Bradycardia may be a symptom in cases of tumor of the brain, hydrocephalus and pellagra. Tachycardia is chiefly found in the terminal stage of a variety of conditions, such as tuberculous meningitis and miliary tuberculosis. The blood pressure is usually normal.

Enlargement of the stomach is frequent, particularly in patients consuming large amounts of fluid. Infants suffering from diabetes insipidus excrete a large amount of the ingested water through the bowels and have symptoms of diarrhea. Enterocolitis is one of the important signs of pellagra. Changes in the gastroenteric tract were observed by Gorke and Deloch, who found hyperacidity and hypersecretion, increased tonus and peristalsis of the stomach and spasticity of the large intestine.

An enlarged liver or spleen may be present in cases of leukemia or xanthomatosis. Anemia, epistaxis, petechiae and the like may also occur with these conditions.

Enlargement of the bladder may be found with any type of severe diabetes insipidus; and enuresis nocturna, which is a frequent and early symptom in childhood, often leads to the correct diagnosis.

The extremities may be disproportionately long in cases in which eunuchoidism is also present. Under these circumstances the delayed epiphysial development may be detected in the roentgenograms. Other changes in bone may be present. Precocious development of the centers of ossification indicate possible involvement of the pineal gland. Osteoperiostitis occurs with congenital syphilis, and destructive changes of the skull, long bones, vertebrae and pelvic bones are seen with xanthomatosis.

When examination of the fingers and toes reveals polydactylism or syndactylism, a developmental defect may be the basis of the disease. Pseudo spina ventosa is seen in cases of Schaumann-Besnier-Boeck disease.

Involvement of the central nervous system has been noted in a great variety of conditions. Vertigo, nausea and vomiting are not only signs of tumor, hydrocephalus, syphilis, leukemia and postencephalitic processes but may be symptomatic of water intoxication, as has been pointed out by Snell and Rowntree. With the same conditions there may be headache, which, however, may be a symptom of idiopathic diabetes insipidus, xanthomatosis or actinomycosis. With actinomycosis and with syphilis persistent occipital pain has also been reported. Convulsions and spasms may occur with tuberculosis, syphilis, postencephalitic conditions, the

terminal stage of tumors and also hereditary diabetes insipidus. The relationship of epilepsy and idiopathic diabetes insipidus, so much discussed in the older literature, is still an interesting question.

General muscular rigidity may be a symptom of tuberculosis, syphilis or tumor. A masklike face is sometimes present in cases of syphilis or of a postencephalitic condition; in the latter tremor may also be found. Staggering gait and ataxia may be seen with tumor and hydrocephalus. Exaggerated reflexes and ankle clonus occur in cases of tumor and also in many cases of "idiopathic" diabetes insipidus. A frequent complaint is insomnia, due not only to thirst and polyuria but to such basic processes as tumor, syphilis, encephalitis and pellagra.

The intelligence of children with diabetes insipidus varies but is generally normal and sometimes supernormal. When it is supernormal the patients are apt to react in an exaggerated manner and are often described as capricious or neurasthenic. However, the symptoms of neurasthenia are also seen with tumor or pellagra. In no case of diabetes insipidus should a neuropathy be taken for granted on account of the psychopathic symptoms. Mental deterioration or mental deficiency may be present in cases of diabetes insipidus due to tumor, syphilis, encephalitis, pellagra or xanthomatosis. In many instances the children have been described as dull and irritable. Mental deficiency may also occur with the hereditary form of diabetes insipidus and when the condition is related to the Laurence-Moon-Biedl syndrome. Depressive states are characteristic of pellagra, tumor or postencephalitic conditions and, particularly in adolescents and adults, may develop into insanity.

A speech defect may accompany the hereditary form of diabetes insipidus or any pathologic process involving the speech centers.

In every case of diabetes insipidus the eyes must be thoroughly examined. Exophthalmos is frequently associated with xanthomatosis and may also be present with tumor or hydrocephalus. Phlyctenulas are seen in cases of tuberculosis and have also been reported to occur with xanthomatosis. Progressive loss of vision, bitemporal homonymous hemianopia, constriction of the visual fields and double vision are symptoms of tumor of the brain, although such a process as xanthomatosis or lymphogranulomatosis may have a similar effect. Examination of the fundus will reveal atrophy of the optic nerve in cases of tumor and also with developmental disturbances such as the Laurence-Moon-Biedl syndrome. In cases of the latter condition retinitis pigmentosa, occurring in conjunction with the atrophy of the optic nerve, will reveal the true nature of the process. Choked disk may be observed with xanthomatosis or tumor and bilateral optic neuritis with idiopathic hydrocephalus. Rigid or unequal pupils may be noted with tuberculosis.

tumor and syphilis, while ptosis, strabismus and nystagmus may occur with these processes as well as with xanthomatosis.

In cases of traumatic diabetes insipidus there is often involvement of the ears, and chronic otitis and deafness have been repeatedly described in reports of xanthomatosis.

The presence of cutaneous lesions may be of diagnostic aid. Dryness of the skin is to be considered a regular symptom of diabetes insipidus. Profuse perspiration has been noted only in the terminal stages of syphilis and tumor. True ichthyosis has been described in the report of a case of hereditary diabetes insipidus. Bronzing of the skin, eczema of various types and particularly xanthomas are of value in the recognition of xanthomatosis; in the final stage of this disease purpura may occur. Erythematous or pigmented desquamating lesions of the exposed parts of the body of an undernourished patient are indications of pellagra. Petechiae and infiltration of the skin may be present in cases of leukemia. In cases of Schaumann-Besnier-Boeck disease there may be sarcoids of the skin.

The importance of the tuberculin test and the Wassermann reaction in the diagnosis of diabetes insipidus needs only to be mentioned.

In cases of symptomatic diabetes insipidus, the basal metabolic rate is usually below —15. The reports of Horrax and Bailey (basal metabolic rate of —38 in a case of tumor) and Whitehead and Darley (basal metabolic rate of —20 with a postencephalitic condition and of —19 after whooping cough) support this statement. According to Rowntree (1924) the basal metabolic rate is not lowered when the disease is idiopathic. One should remember, however, that Rowntree's figures are averages and that an individual rate may behave differently. Thus, Blatt and Greengard reported a basal metabolic rate of + 20 in a case of diabetes insipidus following scarlet fever.

The carbohydrate metabolism during diabetes insipidus was studied by Cowie and others. An increased carbohydrate tolerance has been repeatedly noted by such investigators as Kay, Pacella, Blatt and Greengard and H. H. Turner, while high blood sugar values were reported by Gibson, Magers and Dulaney. Glycosuria is sometimes noted.

The presence of hypercholesteremia is supportive evidence in favor of xanthomatosis, but its absence does not militate against this diagnosis.

A spinal puncture will aid in the diagnosis of tuberculous or syphilitic meningitis and in certain cases will reveal increased intracranial pressure. The therapeutic effect of this procedure will be discussed later.

The value of the roentgenograms of the bones in cases of xanthomatosis has already been discussed. Cysts in the digits may be found

with Schaumann-Besnier-Boeck disease and osteoperiostitis of the long bones with syphilis.

Roentgenograms of the skull are of primary interest. Remnants of skull fractures may be seen in cases of traumatic diabetes insipidus, and projectiles may be located by the roentgenogram. Increase of convolutional markings and separation of the sutures may be found in patients with tumor or hydrocephalus. In such patients a shallow and enlarged sella turcica with or without reduction of the clinoid processes is sometimes seen. Attention may be directed to calcareous masses above, behind and in the sella turcica as evidence of tumor, tuberculoma or gumma.

*Summary.*—From the foregoing discussion it can be seen that while diabetes insipidus is easily recognized as a symptomatic entity, it may be a difficult task to ascertain the underlying process leading to the disturbance in the diencephalopituitary region. In a large number of cases the condition will continue to be unclassified, at least at the present time, since, as revealed by this survey of associated symptoms, much overlapping of these manifestations occurs with the various etiologic forms of diabetes insipidus. Furthermore, weeks or even years may pass before diagnostic signs appear. Diabetes insipidus must be differentiated from temporary polyuria, primary polydipsia, diabetes mellitus and polyuria due to infections of the urinary tract, chronic nephritis or polycystic kidneys. Knowledge of the associated symptoms is therefore of great importance; they are outlined in the table.

## TREATMENT

Diabetes insipidus depending on a pathologic process which can be recognized may be susceptible to etiologic treatment. Thus patients with syphilis should be given the benefit of the usual antisyphilitic measures, although these are not always effective.[74] A combination of antisyphilitic treatment and the administration of posterior pituitary preparations may be successful. In a number of cases the polydipsia and polyuria were not influenced favorably by the antisyphilitic treatment, although other neurosyphilitic symptoms were improved (Touraine, Golé and Bernou).

When the origin is tuberculous or encephalitic, no specific treatment is available.

It has been reported that in cases of xanthomatosis favorable results have followed dietetic and radiologic treatment, but, as has already been mentioned, in certain instances this condition tends to spontaneous arrest. The dietetic management of xanthomatosis consists in the removal

74. Levinson; Meijers; Rowntree, 1924.

*Suggestive Signs of Pathologic Conditions Associated with Diabetes Insipidus*

| Symptoms and Signs Which Aid in Differential Diagnosis | Associated Pathologic Conditions | Comment |
|---|---|---|
| Familial occurrence | Idiopathic-hereditary form | More frequent in males; general health and development usually normal |
| Polydactylism, syndactylism, retinitis pigmentosa, obesity hypogenitalism, retarded mentality | Laurence-Moon-Biedl syndrome or other defect or lesion of diencephalon | |
| History of abortion or miscarriage | Syphilitic involvement of pituitary gland or diencephalon | |
| Trauma of head (usually basal skull fracture) | Injury (hemorrhage or scar formation) of pituitary gland or diencephalon | Diabetes insipidus may follow quickly or after interval of several months; in some cases obesity, failure of sexual development, involvement of cranial nerves |
| Age period | Congenital (hereditary type); early childhood (xanthomatosis); later childhood (tumors, postencephalitic conditions) | |
| General health | With hereditary type, unaffected; with other types, dependent on underlying condition | |
| Body temperature | With inflammatory lesions, elevated; with involvement of hypothalamus, elevated or subnormal | |
| Sexual precocity | Pineal tumor | |
| Retardation of growth | Tumor of brain; xanthomatosis; postencephalitic lesions of diencephalon | |
| Generalized lymphadenitis | Leukemia; xanthomatosis; syphilis; lymphogranulomatosis | |
| Harelip or cleft palate | Developmental defect of diencephalon | |
| Beefy red tongue | Pellagra | |
| Gingivitis, loss of teeth | Xanthomatosis | |
| Necrotic exudate on tonsils | Leukemia | |
| Roentgenograms of lungs | May show characteristic changes in case of tuberculosis, xanthomatosis, sarcoids, leukemia | |
| Cardiac enlargement | Chronic nephritis | Absent with idiopathic-hereditary form |
| Bradycardia | Tumor of brain; hydrocephalus; pellagra | |
| Hepatosplenomegaly | Xanthomatosis; leukemia; chronic nephritis (from cardiorenal disease) | |
| Anemia and hemorrhagic manifestations | Leukemia; xanthomatosis | |
| Roentgenogram of bones | With pineal tumor, advanced epiphysial closure; with Laurence-Moon-Biedl syndrome or other defect or lesion of diencephalon, delayed epiphysial closure; with syphilis or xanthomatosis, characteristic changes | |
| Pseudo spina ventosa | Schaumann-Besnier-Boeck disease (sarcoids) | Other sarcoids in skin, lungs or bones |
| Increased intracranial pressure (nausea, vomiting, headache) | Tumor of brain, xanthomatosis, etc. | Nausea, vomiting and headache occur also in cases of water intoxication |
| Enlargement of head | Tumor of brain, xanthomatosis, etc. | |
| Mental deficiency | Laurence-Moon-Biedl syndrome; encephalitis and other lesions of brain | Intelligence usually normal with idiopathic-hereditary type, but behavior may be capricious or "neurasthenic" |
| Exophthalmos | Xanthomatosis; also perhaps with tumors and hydrocephalus | |
| Loss of vision (atrophy of optic nerves, choked disk) | Tumor of brain, xanthomatosis, etc. | Retinitis pigmentosa with Laurence-Moon-Biedl syndrome |
| Deafness | Trauma (basal fractures); xanthomatosis | |
| Cutaneous lesions | With all forms, dry skin and acrocyanosis; with xanthomatosis, bronzing, xanthomas; with pellagra, typically distributed pigmentation, etc.; with leukemia, infiltrative skin lesions and later purpura; with Schaumann-Besnier-Boeck disease, sarcoids | |
| Basal metabolism | Decreased in many forms | Has been reported as normal with idopathic-hereditary type |
| Hypercholesteremia | Xanthomatosis | Not always present |
| Roentgenograms of skull | With trauma, fracture; with hydrocephalus, increased convolutional markings, separation of sutures, enlargement of ventricles (encephalograms); with xanthomatosis, typical changes; with tumor, distortion of sella turcica, etc. | |

of fat from the diet, a procedure which may lead to reduction of the hypercholesteremia often present.[75] Roentgenotherapy of the diencephalopituitary region has been advocated (Sosman, 1932), and in certain cases beneficial results have been reported (Sparrow and Fetner).

Tumors of the brain causing diabetes insipidus present obvious difficulties in treatment as well as in diagnosis. As previously emphasized, diabetes insipidus may be the first symptom of such a tumor, and it may continue to be the only one for many years. In 1 of our patients (case 2), in whom a tumor was present at the age of 2½ years, the parents refused to permit operation. When seen about eight years later the boy showed no increase in his symptoms, although he was not normal from an endocrine standpoint. Furthermore, many of the general or focal signs of a cerebral new growth may be simulated by other pathologic processes. Decision concerning operation for a tumor of the brain must be made from other criteria than the associated diabetes insipidus.

The necessity and nature of surgical intervention in cases of traumatic diabetes insipidus depend on the type of injury. In the case reported by Marañon and Pintos an unsuccessful attempt was made to remove a projectile lodged in the brain.

In case of hydrocephalus or increased intracranial pressure repeated spinal puncture may perhaps be justified, with the usual precautions which surround this procedure in cases of brain tumor.

Pellagra associated with diabetes insipidus must be treated as a deficiency disease.

In the symptomatic treatment of diabetes insipidus there have been used various preparations of the posterior lobe of the pituitary gland, the most effective being pitressin (Kamm). Frequently the patient is relieved of his most annoying symptoms, polyuria and polydipsia, almost immediately after the first administration of such a preparation. Disappearance of the thirst and lessened frequency of urination enable the child to sleep during the night, to attend school and to carry out his usual activities. Dryness of the mouth and skin also disappears, and a gain of weight and improvement of the child's general condition usually follow.

According to Clausen, administration of solution of posterior pituitary double U. S. P. strength ("surgical pituitrin") to a patient suffering from diabetes insipidus results in a diminution of the volume and a corresponding increase of the specific gravity of the urine; the changes in the elimination of solutes is small as compared with the fluctuation in the volume of urine; the hourly rate of elimination of

75. Bürger; Rowland.

chlorides is always reduced, while that of creatinine and uric acid does not seem to be affected. The urea clearance appears to be diminished (Peters).

Since the administration of various extracts of the posterior lobe of the pituitary gland constitutes asymptomatic treatment, it is not surprising that it has proved effective in cases of varied causation. Success has been reported in cases of hereditary idiopathic diabetes insipidus, in many unclassified cases and in some cases in which the condition was due to miliary tuberculosis (Healy), Hodgkin's disease (Desbuquois), syphilis (Gibson and Martin), xanthomatosis (Wortis, Wolf and Dyke), tumor [76] and trauma (Marañon and Pintos). In none of the cases mentioned is benefit invariably obtained. In some cases in which the disease is due to xanthomatosis it is necessary to increase the dose continuously, and in others the drug is said to be ineffective. Lack of effect has been reported in cases of post-traumatic involvement (J. H. Turner), in a number of cases of syphilis and particularly with postencephalitic conditions.[77] In cases of diabetes insipidus following encephalitis, untoward effects of the treatment have also been noted; water intoxication may result, since the patient continues to drink large amounts of fluid while the output of water is reduced by the medication (Snell and Rowntree). Postinfectious encephalitic conditions seemingly respond better to pitressin (Thompson and Johnson) than those following epidemic encephalitis.

Subcutaneous administration of pituitrin or pitressin was stated by Nobécourt and Ducas to be effective in 95 per cent of the cases. It is the most effective method of treatment, although open to the objection that it requires repeated injections at short intervals. Untoward effects, some of which occur immediately or within fifteen to thirty minutes after injection, are vasomotor reactions, pallor, increased blood pressure, intestinal cramps, colic, spastic diarrhea and nausea.[78] Anaphylactic reactions, occurring some time after the injection, have also been reported (Forró and Lendvai). Local atrophy of fat sometimes follows the repeated injections (Harmeier and Finney).

There is no cumulative effect of extracts of the posterior lobe of the pituitary gland. Although they reduce the polyuria, an overdose does not cause oliguria nor, as a matter of fact, reduction of the urinary output below a normal level.

The dose of pitressin must be adjusted to the individual patient. If the administration of 1 to 3 cc. of pitressin per day divided into two

76. Horrax and Bailey; Moffett and Greenberger; Römer; Rosenbloom.
77. Biggart, 1937; Mensi; Roehm; Signorelli.
78. Souques and others; Spohn.

or three doses proves effective, larger doses are seldom of benefit. The effect of the dose as a rule lasts four to six hours, sometimes fourteen to sixteen hours and in certain cases one to two days. Reports of permanent cure after pituitary treatment [79] are hard to reconcile with the known temporary pharmacologic mechanism of the extracts and with the nature of diabetes insipidus, although reports of transitory diabetes insipidus have to be taken into consideration (Eaves).

The intranasal application of solution of posterior pituitary ("pituitrin O, obstetrical pituitrin") was first recommended by Blumgart. It is a valuable addition to the measures available for the symptomatic treatment of diabetes insipidus. Rather than a solution of posterior pituitary, a solution of pitressin should be applied intranasally as a spray or by means of a gauze tampon; as a rule, when the substance is given in this way, the dose must be larger than when administered subcutaneously. A powder of the posterior lobe of the pituitary gland may be taken as a snuff several times a day, about 50 mg. being the average dose.[79a] This method of treatment is preferred by many patients. Occasionally response is better to intranasal administration than to subcutaneous injection. Before recommending intranasal treatment it should be ascertained that no obstacle prevents the powder from reaching the inner and higher parts of the nose.[80] Nasal applications may be helpful for several years, without development of any sign of intolerance.

Administration of posterior pituitary preparations by mouth or by rectum has not been found of practical value.

A number of drugs besides posterior pituitary preparations have been used in the treatment of diabetes insipidus. Ergotine as an antidiuretic has been entirely replaced by posterior pituitary preparations. Nevertheless, it is of at least theoretic interest that this substance was widely used with apparent success in the treatment of diabetes insipidus during the nineteenth century.[81] It is possible that posterior pituitary preparations and ergotine not only have a similar effect on the uterine muscle but also exert the same pressor effect. Lacy employed fluid extract of ergotine, giving ½ drachm (1.94 Gm.) four times daily to a boy of 12 years. In this particular case the output of urine was reduced from 4 or 5 liters to 2 liters or less. In spite of these experiences with ergotine it is not to be recommended for practical use at the present

79. Denéchau and Mandroux; Weiss.

79a. Choay, A., and Choay, L.: Traitement du diabète insipide par des inhalations d'extrait de lobe postérieur d'hypophyse, Rev. neurol. **31**:267, 1924. Smith, F. M.: Treatment by Intranasal Insufflation of Posterior Lobe Powder, J. A. M. A. **102**:660 (March 3) 1934.

80. Lereboullet and Bernard; Nobécourt and Ducas.

81. Case; Da Costa; Lacy.

time, since preparations of ergot are variable in composition and unstable as well as relatively ineffective when compared with posterior pituitary preparations.

Certain extracts of endocrine glands other than those from the posterior pituitary lobe have been used in the treatment of diabetes insipidus. Intermedin (from the pars intermedia) is said to have a favorable effect on thirst and diuresis. Although the response does not seem to be so great as that obtained by equal amounts of solution of posterior pituitary, intermedin is preferred by some patients on account of the absence of pressor effects (H. H. Turner). Gonadotropic substance from the urine of pregnant women (antuitrin-S) administered to a child with bilateral cryptorchidism and diabetes insipidus was said to have resulted in the cure of the latter as well as descent of the testes (Allen and Stokes). Estrogen has also been used, particularly in treatment of adults, and has been found effective in a number of instances.[82] The administration of testicular extract has been reported.[83] Corpus luteum extract was said to be effective in a case of diabetes insipidus in a girl with delayed menstruation (Meyer-Nobel). In a number of cases insulin has been administered, apparently with some benefit.[84]

Valerian (Reith) and opium are seldom administered at the present time, but there are numerous reports of the beneficial effects of aminopyrine, antipyrine and acetylsalicylic acid.[85] They relieve subjective symptoms, reduce thirst and polyuria to a certain extent and increase the specific gravity of the urine. Owing to the possibility of agranulocytosis, the continued use of aminopyrine is not advisable. Phenobarbital or other sedatives enable the patient to sleep.

Among dietary measures, restriction of sodium chloride and of protein has been particularly emphasized. According to Allen and Sherrill, continuous reduction of sodium chloride in the urine to a fraction of a gram per day is required for successful treatment. Restriction to this degree is well tolerated. In cases of severe involvement, however, radical restriction of protein is necessary if dietary measures only are used. It is evident that such treatment cannot be continued long in the case of a growing child and that during the period of growth dietary methods can be used only in conjunction with other forms of therapy.

In many cases spinal puncture has a favorable effect on the symptoms of diabetes insipidus. This procedure, first recommended by Herrick,

82. Beltrametti; Duvoir and others; Troisier.

83. Beltrametti; Rothmann.

84. Avellone; Wentzler.

85. Eichorst; Kahn; Scherf.

has often been used successfully.[86] It is surprising that there have been occasional reports of lasting beneficial effects after the removal of 8 to 15 cc. of spinal fluid from patients with normal intraspinal pressure. In cases of increased pressure due to lymphogranulomatosis (Desbuquois) a reduction of the urinary output from 14 to 5 liters has been observed after spinal puncture. The danger of sudden release of intracranial pressure in cases of tumor of the brain should be remembered. There are reports of the alleviation of diabetes insipidus after encephalographic examination of mentally deranged patients (Schube)

Success has been reported after the parenteral injection of milk (Hatzieganu and Hanganutziu). Hydrotherapy (Rochlin) has been employed to reduce the polyuria and polydipsia by sweating. Short wave treatment of the tuberopituitary region is said to have reduced the polyuria from 7 to 2 liters in a case of traumatic diabetes insipidus (Drouet, Vérain, Grandpierre and Pierquin).

Certain experiments on transplantation may be mentioned. In 1936 Hirsch and Demel reported the cure of traumatic diabetes insipidus by the abdominal implantation of a human hypophysis. In another case of traumatic diabetes insipidus, the posterior lobe of a human hypophysis obtained from a person of the same blood group but of different sex was successfully transplanted by Hirsch into the rectus muscle of the patient. The polyuria was much reduced, and results of the concentration and dilution tests resembled those obtained for a normal person. Implantation of the pituitary glands of a sheep into a young patient was said to have resulted in transitory relief (Hirsch, 1937). These encouraging results, however, were obtained in cases of traumatic diabetes insipidus, a type which sometimes tends to spontaneous improvement.

Removal of an adenoma of the thyroid gland from a patient suffering with diabetes insipidus resulted in marked temporary amelioration of the polyuria and polydipsia (McConnell). On the contrary, in a case of diabetes insipidus due to syphilis, complete thyroidectomy was not followed by any striking diminution of the urinary output (Findley and Heinbecker).

Several instances of the incidental termination of the symptoms of diabetes insipidus by physiologic or pathologic processes have been reported. In Silvestri's case diabetes insipidus which was resistant to pituitary and thyroid treatment had been present since the boy was 4 years of age; when the testes descended, at the age of 20 years, the polyuria disappeared. Strauss reported a case in which the symptoms

86. Cammidge; Christie and Stewart; Graham; Signorelli; Tucker.

of diabetes insipidus disappeared when the signs of myxedema appeared, and Harvey, a case in which cessation of symptoms followed an attack of measles.

*Summary.*—The underlying pathologic process sometimes responsible for diabetes insipidus is in some instances susceptible to treatment. This may obtain in cases of syphilis, xanthomatosis, tumor of the brain, traumatic lesions, pellagra and some forms of hydrocephalus. Spinal puncture may have its indications. Symptomatic treatment consists largely of the use of extract of the posterior lobe of the pituitary gland (preferably pitressin) administered by injection or intranasally. A number of other substances and drugs have been advised from time to time.

## REPORT OF CASES

CASE 1.—K. H., a girl 10 years of age, was admitted to the Children's Hospital on April 16, 1936, with symptoms of extreme thirst and frequent urination of nine months' duration. After drinking large quantities of water the girl felt nauseated, but she had vomited only once. She suffered from headaches and anorexia. She had had German measles and mumps at the age of 7 years and chickenpox at 8 years; tonsillectomy had been performed at 6 years.

The paternal grandmother had had diabetes mellitus. On the mother's side the family history was somewhat vague. The mother herself was nervous and had had goiter; a maternal aunt and the maternal grandmother had had uterine tumors and were "hysterical." A maternal uncle had a "nervous heart," and another had had persistent "jerky movements."

On April 20 the following positive findings were noted: The skin was dry and scaly; there was mild obesity of the Fröhlich type. The important negative findings were normal distribution of hair, normal genitalia, absence of enlargement of the thyroid, normal teeth except for considerable caries, normal body measurements, absence of abnormalities on physical examination of the heart, lungs and abdomen, normal reflexes (except for Oppenheim's sign), absence of paralyses and normal ocular fundi.

The fluid intake was between 3 and 4 liters and the urinary output between 2 and 4 liters daily. The urine was light in color, with a specific gravity of 1.004 and an alkaline reaction; no albumin or sugar was present; the dilution test yielded specimens with a specific gravity between 1.002 and 1.006, but in the concentration tests the value was as high as 1.013. The phenolsulfonphthalein test showed excretion of 30 per cent in the first hour and 27.5 per cent in the following hour, with a total of 57.5 per cent. The urea clearance was 77 per cent in the first hour and 60 per cent in the second hour. There were 4,410,000 red cells per cubic millimeter and 4,100 white cells, 58 per cent of which were polymorphonuclear leukocytes, 34 per cent lymphocytes, 6 per cent large mononuclears and 2 per cent eosinophils. The inorganic phosphorus content of the serum was 4.7 mg. per hundred cubic centimeters, serum calcium 9.4 mg., urea nitrogen 10.5 mg. and nonprotein nitrogen 22 mg. The total protein content of the serum was 7.54 Gm. per hundred cubic centimeters, the albumin 4.8 Gm. and the globulin 2.74 Gm.; the albumin-globulin ratio was 1.75. The chlorides of the whole blood amounted to 429 mg. as sodium chloride. The venous blood showed 72 mg. of sugar per hundred cubic centimeters. The basal metabolic rate was —7.5. Both Wassermann and tuberculin reactions were negative.

The stereoscopic roentgenograms of the skull showed no evidence of pathologic changes of the bone; the sella turcica was normal.

In this case the condition could not be classified. At first pitressin jelly was given by nasal insufflation, but no definite response was noted within a week. When pitressin was administered subcutaneously (0.5 cc. three times daily) the fluid intake was reduced to 1,470 cc. and the urinary output to 2,100 cc. However, complaints of abdominal pain and nausea followed the injections, and the dose of pitressin was reduced to 0.3 cc. given three times a day; this dose kept the intake and output of water within normal limits and reduced the complaints. In order to make the child independent of injections, nasal insufflation of powdered posterior pituitary lobe (25 mg. six times daily) was given. With this treatment the fluid intake and output were between 2 and 3 liters a day. On May 30, at the parents' request, the patient was discharged in good general condition; she was advised to continue nasal insufflation and to return to the referring physician for regular examination.

Several times during the following year the child was brought to the outpatient clinic for study. At first improvement of the polydipsia and polyuria was evident. In June the daily urinary output was between 1,200 and 2,250 cc., the specific gravity reaching a value of 1.010. The treatment then consisted of seven insufflations of posterior pituitary powder daily. Periods of headache alternated with periods of no complaint. Sometimes there was such a rapid change in the child's behavior that a neurotic or hysterical condition was simulated. In October the patient was doing well although complaining of headaches; the output of urine was between 2 and 2.5 liters daily with four daily insufflations of posterior pituitary powder. In December she returned again with a complaint of headache. Examination of the eyegrounds showed that the vessels and maculas were normal, but there was a questionable elevation of vessels at the border of the disks. The visual fields were normal. The nose and paranasal sinuses were apparently normal. Admission to the hospital was recommended but was refused.

The child was not seen again until June 1937. She had lost weight and had a low grade fever; she appeared pale and emaciated; otherwise the physical examination gave negative results. The urinary output in twenty-four hours was only 450 cc. The reaction to tuberculin was negative. Admission to the hospital was recommended but was postponed by the parents.

On July 19 the child was admitted to Christ Hospital in Cincinnati. On physical examination there she appeared chronically ill. On examination of the eyes, both pupils were found to be dilated; the right pupil did not react to light. The disks showed marked atrophy on the right and partial atrophy on the left without choking; the left temporal field of vision was grossly constricted. The examination of the heart, lungs and abdomen showed no abnormalities. Babinski's and Oppenheim's reflexes were present. The stereoscopic roentgenograms of the skull made in various positions showed no evidence of bone disease; the convolutional markings on the internal table of the skull were slightly more prominent than normal; the sella turcica and clinoid processes were normal. A tentative diagnosis of craniopharyngioma was made, and frontal craniotomy was recommended.

The operative technic and findings were as follows: Frontal craniotomy was done on the right. There was found an irregular, somewhat pinkish mass growing from the base of the chiasm and extending upward about both optic nerves. This mass was dissected free from the optic nerve on the right and as far beneath the chiasm as possible. An attempt was made to aspirate it, but no fluid was obtained. The capsule was then incised. The mass was found to be soft and

semi-fluid; it could not be removed. As far as possible, this mass was macerated with a staphylorrhaphy dissector and then sucked from its position. Complete removal of the tumor would not have been possible without sacrifice of both optic nerves and probable invasion of the third ventricle. No difficulty was encountered with hemorrhage. The dura was then closed, a flap was replaced in layers, and the bone flap was anchored in place with two wires.

The patient had a normal postoperative course until August 6, when hemolytic streptococcic infection of the wound in the scalp developed. This responded to treatment fairly well, but the patient failed to improve. Transfusions and fluids were administered intravenously, but to no avail. The patient was discharged unimproved on August 25 and died several days later at home. Necropsy was not performed.

On microscopic examination, the excised tissue was found to be composed of rather dense glial fibers supporting a few small round cells. Larger rounded or oval cells, roughly of the same size and possessing either clear vesicular nuclei or densely chromatic nuclei, were also present. The cells showed little differentiation. Dr. Vonderahe, who studied the sections, diagnosed the tumor as a primitive neuroganglioma derived from glial cells.

Case 2.[87]—W. A., a boy, had shown the symptoms of polydipsia and polyuria before the age of 1 year. When seen at the age of 2½ years he was drinking as many as fifteen to twenty glasses of water a day and frequently voiding large amounts. His birth had been normal and his birth weight was 7 pounds (3,175 Gm.). It was stated that his head was large in the first year of life. He did not stand until 18 months of age or walk until 2 years old; it was said that he used a few words at 9 months. His anterior fontanel closed only at the age of 2 years and 3 months. His penis began to enlarge about six months before this visit. Generalized convulsions began at the age of 2 years and recurred every two weeks to two months. The boy's father and mother and three siblings were living and well.

The patient was big for his age, weighing 35 pounds (15.9 Kg.) and being 38 inches (97 cm.) tall. The penis was unusually large, and the testicles were somewhat larger than the average (fig. 1). A few axillary and pubic hairs were present. The head measured 20¾ inches (52.7 cm.) in circumference. No ocular paralyses were present; there was no paralysis of the extremities or facial muscles, nor were there any changes in reflexes. Vision was normal, and the eyegrounds showed no alteration.

The parents refused to admit the boy to the hospital for further study. However, a specimen of urine was obtained; it was pale, with a specific gravity of 1.002, absence of albumin and sugar and negative microscopic findings. Blood obtained at this visit gave a negative Wassermann reaction. Stereoscopic roentgenograms of the skull showed a calcified tumor or a bony growth immediately above the floor of the skull, just anterior to the sella turcica, and a curved line of calcification which extended upward, slightly forward and then backward. The nature of the latter lesion can only be surmised; it suggested a calcified tumor, or rather the capsule of one, or perhaps calcification of an old hemorrhage (fig. 2). Ossification and epiphysial development of the wrist were within normal limits.

87. Previously reported by Griffith, J. P. C., and Mitchell, A. G.: The Diseases of Infants and Children, ed. 2, Philadelphia, W. B. Saunders Company, 1937, p. 1078.

Fig. 1 (case 2).—W. A. at the age of 2½ years.

Fig. 2 (case 2).—Roentgenogram of the skull of W. A. Arrows point to the calcified areas.

The endocrine symptoms in this case may have been due to involvement of the pineal gland or to overaction of the growth-promoting and gonadotropic factors in the pituitary gland; the diabetes insipidus may have been caused by the disturbance in the diencephalopituitary region.

The patient was seen again briefly when he was 11 years of age. Polyuria and polydipsia had continued; he had had an occasional convulsion. Hospitalization was again refused. At the time of this visit the boy's height was 58 inches (147 cm.), his weight 105 pounds (47.6 Kg.) and the circumference of his head 22½ inches (57 cm.). Mentally he was sluggish. A record of an intelligence test performed at the age of 8 years and 7 months showed that his mental age at that time was 5 years and 8 months. The genitalia had continued to develop;

Fig. 3 (case 2).—W. A. at the age of 11 years.

pubic and axillary hair had been present for several years; there was some growth of hair on the face, and marked acne was present, particularly on the chest (fig. 3). No evidence of masturbation had been observed by the parents, nor did the boy show particular interest in girls. The voice was deep. Vision was normal, and the eyegrounds showed no change. Roentgenograms of the wrists showed complete epiphysial closure (fig. 4).

Case 3.—C. A. K., a girl 4 years of age, was admitted to the Children's Hospital on Dec. 6, 1937. The chief complaints were extreme thirst and frequent urination. Three months previously the child had started to drink excessive amounts of water and to wet the bed, although proper toilet habits had been established for three years. She drank and voided every fifteen minutes during

the day and several times during the night. Before admission to the hospital the amount of urine excreted had been more than 6 quarts (5.7 liters) daily. She lost appetite and weight; she had complained of dizziness and pain in the stomach but not of headaches or vomiting. She had received "tablets of pituitary gland" without benefit. Later, pitressin was injected every other day in doses of 0.5 cc. While at first the injections seemed beneficial, later they had no noticeable effect.

The mother reported that labor had been prolonged, the membranes rupturing about nine hours before delivery. In the first three years of life the child had been in perfect health. Ten months before admission to the hospital she had had a cough, high fever and generalized convulsions lasting about ten minutes and had passed black stools.

Both the father, 40 years of age, and the mother, 36 years of age, were in good health. One older sister, 7 years of age, weighed 69 pounds (31.3 Kg.) and showed moderate obesity of the Fröhlich type. A second cousin of the father had a harelip.

The following positive findings were noted: slight enlargement of the head (3 cm. greater in circumference than average for the age), elevation of the skull

Fig. 4 (case 2).—Roentgenogram of the right wrist of W. A. at the age of 11 years.

in the region of the frontal suture, evidence of recent loss of weight and dry skin. Negative findings of importance were normal distribution of hair, normal genitalia, absence of thyroid enlargement, normal body measurements, normal teeth, absence of abnormalities on physical examination of the heart, lungs and abdomen, normal reflexes, absence of paralysis, normal mentality and normal ocular fundi.

The fluid on the first day in the hospital was 9,040 cc., while the urinary output was 4,600 cc. On the next day the fluid intake was 8,200 cc. and the urinary output 4,650. The urine was pale, its reaction alkaline and its specific gravity between 1.002 and 1.004; neither albumin nor sugar was present; the sediment was normal. The urea clearance test gave a value of 106 per cent in the first period and 93 per cent in the second period. The phenolsulfonphthalein test showed excretion of 42 per cent in the first twenty minutes, 19 per cent in the following fifteen minutes, 17 per cent in the next thirty minutes and 8 per cent in the next sixty minutes. The blood urea nitrogen level was 9 mg. per hundred cubic centimeters. The Wassermann reaction was negative.

The stereoscopic roentgenograms of the skull showed no evidence of bone disease; the sella turcica was normal. The child had no fever during her stay in the hospital. At first she was exhausted from lack of sleep. On the third day

after admission to the hospital, injections of 0.5 cc. of pitressin were given twice daily. Within twenty-four hours the fluid intake decreased to 3,020 cc. and the urinary output to 1,800 cc. Twenty-four hours later the fluid intake was 1,020 cc., and the urine amounted to 1,065 cc. On the third day, the fluid intake was 3,080 cc. and the urinary output 1,060 cc. Later pitressin in jelly was applied intranasally but without much effect, the water intake immediately going up to 5,080 cc. and the urine output to 2,560 cc.; the next day the intake was 6,840 cc. and the output 3,550 cc. The injections of pitressin were resumed, and the child was discharged from the hospital.

No underlying cause for the diabetes insipidus could be determined during the child's stay in the hospital. Her physician was advised to reexamine the ocular fundi frequently and to have roentgenograms of the skull made at regular intervals.

CASE 4.—R. H., a boy 8 years of age, was admitted to the Children's Hospital on Nov. 14, 1937. He had apparently suffered from birth from excessive thirst, frequent urination and persistent enuresis; he craved sweets; his appetite was poor. At the age of 22 months several bones had been fractured in an automobile accident. In roentgenograms taken several months later it was found that the right lung was collapsed, subsequent roentgenograms showing that expansion had taken place. Convulsions had occurred several years before admission and pyelitis a few months before. The patient's father and mother were living and well; four siblings had died of various causes; four were living and well.

On physical examination, the boy was found to be average in size but overweight. The positive findings were hypertrichosis of the back and extremities and increased space between the upper central incisors. Negative findings of importance were absence of dryness of the skin, absence of pubic and axillary hair, normal external genitalia, normal body measurements, absence of abnormalities on physical examination of the heart, lungs and abdomen, normal reflexes, absence of paralyses, normal mentality and normal ocular fundi.

The stereoscopic roentgenograms of the chest showed nothing abnormal. The stereoscopic roentgenograms of the skull showed no evidence of pathologic changes; the sella turcica was normal. Roentgenograms showed no evidence of disease of the long bones. The fluid intake was between 3 and 4 quarts (2.83 and 3.78 liters) daily, and the urinary output about the same. The urine was alkaline, clear and slightly colored and had a specific gravity between 1.003 and 1.008; albumin was not present, and sugar was found at 1 test only; the sediment was normal. When the fluid intake was restricted for three days the specific gravity of the urine rose to 1.022. The urea clearance was 98 per cent in the first hour and 137 per cent in the second hour. The phenolsulfonphthalein excretion was 32 per cent in the first fifteen minutes, 18 per cent in the following thirty minutes, 16 per cent in the next hour and 16 per cent in the next two hours. Dextrose tolerance tests were done three times without showing definitely abnormal curves. The blood sugar levels during fasting were 93, 100, 120 and 91 mg., respectively, per hundred cubic centimeters. The blood calcium level was 10.4 mg. per hundred cubic centimeters, and the blood chlorides amounted to 573 mg. as sodium chloride. The total serum protein value was 8.09 Gm., the albumin 5.17 Gm. and the globulin 2.92 Gm.; the albumin-globulin ratio was 1.77. The nonprotein nitrogen content was 30 mg. per hundred cubic centimeters. The leukocyte count was 12,200; there were 51 per cent polymorphonuclears, 1 per cent basophils, 2 per cent eosinophils, 38 per cent lymphocytes and 8 per cent monocytes. The Wassermann reaction of the blood was negative, as was the Kahn reaction of the spinal fluid.

The spinal fluid contained no cells, and the reaction to Pandy's test was negative. The reaction to tuberculin was negative.

In this case a definite diagnosis of diabetes insipidus could not be made, since the kidneys showed ability to concentrate the urine. A diagnosis of primary polydipsia was not acceptable because no other neurotic symptoms were present. Diabetes mellitus was ruled out by the results of the dextrose tolerance test. Spinal puncture did not influence the water metabolism.

At first 1 cc. of pitressin was given twice a day in nasal packs, but without effect. Later the drug was given subcutaneously in increased doses, and a definite response was obtained when 3 cc. was given daily, the fluid intake and urinary output being reduced to 2 quarts (1.9 liters). When the injections were discontinued, the intake and output went up to 4 quarts again. Thus a response to pitressin was definitely obtained, although large doses were required. At present the child continues to be under observation.

## BIBLIOGRAPHY


Achard, C., and Ramond, L.: Potomanie chez un enfant, Bull. et mém. Soc. méd. d. hôp. de Paris **12**:380, 1905.

Adlersberg, D.: Dauertherapie des Diabetes insipidus, Ztschr. f. klin. Med. **128**: 598, 1935.

Adolph, E. F., and Ericson, G.: Pituitrin and Diuresis in Man, Am. J. Physiol. **79**:377, 1927.

Alberti: Singolari alterazioni scheletriche in un caso di infantilismo ipofisario, Radiol. med. **11**:517, 1924.

Allen, A. A., and Stokes, J. S.: Cure of Diabetes Insipidus Coincident with Bilateral Correction of Abdominal Cryptorchidism by the Gonadotropic Factor from Pregnancy Urine, J. A. M. A. **106**:780 (March 7) 1936.

Allen, F. M., and Sherrill, J. W.: Diet Treatment of Diabetes Insipidus, J. Metab. Research **3**:479, 1923.

Angelini, V.: Diabete insipido e oliguria centrale quali complicazione del morbillo, Clin. pediat. **12**:990, 1930.

Anspach, W. E.: Xanthomatosis with Involvement of Vertebral Body, Am. J. Dis. Child. **48**:346 (Aug.) 1934.

Atkinson, F. R. B.: Schüller-Christian's Disease, Brit. J. Child. Dis. **34**:28, 1937.

Avellone, U.: Osservazioni e ricerche su due casi di diabete insipido, Arch. ital. di pediat. **2**:488, 1934.

Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

Bandler, V.: Beitrag zur Aetiologie des Diabetes insipidus, Arch. f. Dermat. u. Syph. **41**:49, 1897.

Baráth, J., and Weiner, P.: Disturbance of Water Metabolism and the Role of Physicochemical Factors in Diabetes Insipidus, Orvosi hetil. **79**:917, 1935; abstracted, Zentralbl. f. Kinderh. **31**:253, 1935.

Barnes, B. O.; Regan, J. F., and Bueno, J. G.: Is There a Specific Diuretic Hormone in the Anterior Pituitary? Am. J. Physiol. **105**:559, 1933.

Bartels, M.: Ueber Plattenepithelgeschwülste der Hypophysengegend (des Infundibulums), Ztschr. f. Augenh. **16**:407, 1906.

Bauer, R.: Zur Pathologie und Differentialdiagnose von "Diabetes insipidus" und primärer Polydipsie, Wien. Arch. f. inn. Med. **11**:201, 1925.

Belkowski, J.: Actinomycose de la base du crâne et des méninges; diabète insipide, Rev. de méd., Paris **31**:415, 1911.

Beltrametti, L.: Die Sexualfunktionen in ihren Beziehungen zum Wasserhaushalt, insbesondere zum Diabetes insipidus, Endokrinologie **16**:241, 1935.

Bernard, C.: Leçons de physiologie expérimentale appliquée à la médecine, Paris, J.-B. Baillière, 1855.

Bernhardt, H.: Ein Beitrag zur Laurence-Biedlschen Krankheit, Ztschr. f. klin. Med. **107**:488, 1928.

Beumer, H.: Diabetes Insipidus, in von Pfaundler, M., and Schlossmann, A.: The Diseases of Children, translated by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935, vol. 2, p. 350.

Biasotti, A.: Thyroïde et action diurétique de l'extrait antéhypophysaire, Compt. rend. Soc. de biol. **115**:329, 1934.

Biedl, A.: Innere Sekretion, Berlin, Urban & Schwarzenberg, 1913.

Physiologie und Pathologie der Hypophyse, Munich, J. F. Bergmann, 1913.

Biggart, J. H.: Diabetes Insipidus, Brain **58**:86, 1935.

Anatomic Basis for Resistance to Pituitrin (Posterior Pituitary Preparation), J. Path. & Bact. **44**:305, 1937.

Blatt, M. L., and Greengard, J.: Diabetes Insipidus: Report of a Case in a Child, Arch. Pediat. **43**:811, 1926.

Blumgart, H. L.: Antidiuretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus, Arch. Int. Med. **29**:508 (April) 1922.

Bourquin, H.: Studies on Diabetes Insipidus: Diuretic Substance; Preliminary Observations, Am. J. Physiol. **83**:125, 1927.

Studies on Diabetes Insipidus: Diuretic Substance; Further Observations, ibid. **88**:519, 1929.

Burger, in Klemperer, G., and Klemperer, F.: Neue deutsche Klinik, Berlin, Urban & Schwarzenberg, 1934, vol. 12, p. 583.

Bulloch, W.: Diabetes Insipidus, in Treasury of Human Inheritance, University of London, Francis Galton Laboratory for National Eugenics, Eugenics Laboratory Memoir 6, 1909, pt. 1, sect. 1a.

Burgess, W. W.; Harvey, A. M., and Marshall, E. K., Jr.: Site of Antidiuretic Action of Pituitary Extract, J. Pharmacol. & Exper. Therap. **49**:237, 1933.

Cammidge, P. J.: Complete Recovery from Diabetes Insipidus, Practitioner **105**: 244, 1920.

Campbell, J. R., and Blumgart, H. L.: Treatment of Diabetes Insipidus with Pituitary Posterior Lobe Extract Applied Intranasally, Am. J. M. Sc. **176**: 769, 1928.

Camus, J., and Roussy, G.: Hypophysectomie et polyurie expérimentales, Compt. rend. Soc. de biol. **75**:483, 1913.

Diabète insipide expérimental et opothérapie hypophysaire, ibid. **83**:1578, 1920.

Experimental Researches on the Pituitary Body: Diabetes Insipidus, Glycosuria and Those Dystrophies Considered as Hypophyseal in Origin, Endocrinology **4**:507, 1920.

Carter, A. H.: Case of Diabetes Insipidus Treated with Ergot of Rye, Birmingham M. Rev. **12**:264, 1882.

Case, W. N.: Effect of Ergot in a Case of Polyuria, Detroit Clin. **1**:89, 1882.

Catini, V.: Su di un caso di diabete insipido in bambina eredoluetica, Prat. pediat. **11**:275, 1933.

Charcot, 1860, cited by Eichhorn.

Chase, L. A.: Hereditary Diabetes Insipidus, Canad. M. A. J. **17**:212, 1927.

Chavanis, 1887, cited by Eichhorn.

Chester, W.: Ueber Lipoidgranulomatose, Virchows Arch. f. path. Anat. **279**: 561, 1930.

——and Kugel, V. H.: Lipoidgranulomatosis (Type, Hand-Schüller-Christian): Report of a Case, Arch. Path. **14**:595 (Nov.) 1932.

——and Spiegel, L.: Hereditary Diabetes Insipidus, J. A. M. A. **100**:806 (March 18) 1933.

Chiari, H.: Die generalisierte Xanthomatose vom Typus Schüller-Christian, Ergebn. d. allg. Path. u. path. Anat. **24**:396, 1931.

Chown, B., and Lee, M.: Renal Rickets and Dwarfism as Pituitary Disease, Am. J. Dis. Child. **53**:117 (Jan., pt. 1) 1937.

Christian, H. A.: Defects in Membranous Bones, Exophthalmos, and Diabetes Insipidus: An Unusual Syndrome of Dyspituitarism; a Clinical Study, in Contributions to Medical and Biological Research, Dedicated to Sir William Osler, New York, Paul B. Hoeber, 1919, vol. 1, p. 391.

Christie, C. D., and Stewart, G. N.: Study of Some Cases of Diabetes Insipidus with Special Reference to the Detection of Changes in the Blood When Water Is Taken or Withheld, Arch. Int. Med. **29**:555 (May) 1922.

Cignolini, P.: Effetti locali e generali della radioterapia in un caso di diabete insipido associato ad osteopatia (nota preventiva), Radiol. med. **16**:16, 1929.

Clausen, S. W.: Effect of Injections of Pituitary Solution on the Urinary Output in a Case of Diabetes Insipidus, Am. J. Dis. Child. **16**:195 (Sept.) 1918.

Clay, R. H.: Three Cases of Diabetes Insipidus in One Family, Lancet **1**:1188, 1889.

Comby, J.: Xanthomatose, syndrome de Schüller-Christian, Arch. de méd. d. enf. **38**:487, 1935.

Cowie, D. M.: Case of Diabetes Insipidus in a Girl of Ten Years from the Standpoint of Endocrinal Involvement, Am. J. Dis. Child. **18**:194 (Sept.) 1919.

Cushing, H.: Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Co., 1912.

Concerning Diabetes Insipidus and the Polyurias of Hypophyseal Origin, Boston M. & S. J. **168**:901, 1913.

Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

Posterior Pituitary Activity from Anatomical Standpoint, Am. J. Path. **9**:539, 1933.

——and Martin, P.: Primary Gliomas of Chiasm and Optic Nerves in Their Intracranial Portion, Arch. Ophth. **52**:209 (May) 1923.

Da Costa, J. M.: Case of Diabetes Insipidus Successfully Treated by Ergot, M. News, Philadelphia **42**:72, 1883.

Daneri, J.: Diabetes Insipida, Rev. chilena de pediat. **5**:306, 1934.

Deebrey: Observation de polyurie, Gaz. d. hôp., 1859, p. 546.

DeGowin, E. L.: Urinary Concentration in Diabetes Insipidus: Comparison of the Effects of Several Drugs, Am. J. M. Sc. **190**:747, 1935.

Deleonardi, S.: Nachweis der oxytocischen, blutdrucksteigernden und diuresehemmenden Komponenten des Hypophysenhinterlappensekretes im Liquor cerebrospinalis, Arch. f. exper. Path. u. Pharmakol. **180**:135, 1936.

Delpierre, 1861, cited by Eichhorn.

Demme: Ein Fall von Diabetes insipidus, abstracted, Jahrb. f. Kinderh. **14**:437, 1879.

Denéchau, D., and Mandroux, J.: Deux cas de diabète insipide guéri par les injections d'extraits de lobe posteriéur d'hypophyse, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:561, 1924.

Denzer, B. S.: Defects in Membranous Bones, Diabetes Insipidus and Exophthalmos, Am. J. Dis. Child. **31**:480 (April) 1926.

Denzler, E.: Ueber eine eigenartige Form der Dystrophia adiposogenitalis, Jahrb. f. Kinderh. **107**:35, 1924.

Desbuquois, G.: Sur un cas de lymphogranulomatose maligne compliquée de diabète insipide, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1355, 1935.

Doyle, J. B., and Kernohan, J. W.: Ganglioneuroma of the Third Ventricle with Diabetes Insipidus and Hypopituitarism, J. Nerv. & Ment. Dis. **73**:55, 1931.

Drouet, P. L., and Hamel: Diabète insipide chez un hérédosyphilitique, Rev. méd. de l'est **59**:661, 1931.

——Vérain, M.; Grandpierre, G., and Pierquin: Un cas de diabète insipide avec glycosurie: Traitement par les ondes courtes sur la région hypophysotubérienne, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:115, 1936.

Duvoir, M.; Pollet, L., and Cachin, M.: Diabète insipide suivie de diabète sucré avec coma: Influence des grossesses sur la polyurie; traitement par folliculine, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1444, 1932.

Dwyer, H. L.: Child with Congenital Syphilis and Diabetes Insipidus Presenting Syndrome of Corpora Striata Lesion, M. Clin. North America **7**:1201, 1924.

Eaves, E. C.: Diabetes Insipidus, Brain **53**:47, 1930.

——and Croll, M. M.: Pituitary and Hypothalamic Region in Chronic Epidemic Encephalitis, ibid. **53**:56, 1930.

Ebstein, W.: Beiträge zur Lehre vom Diabetes insipidus, Deutsches Arch. f. klin. Med. **95**:1, 1909.

Egler, 1923, cited by Henschen.

Ehrmann, R.: Familiärer Diabetes insipidus bei 3 geistig zurückgebliebenen Kindern, Berl. klin. Wchnschr. **48**:496, 1911.

Eichhorn, G.: Ueber Diabetes insipidus im Kindesalter, Jahrb. f. Kinderh. **42**: 44, 1896.

Eichorst, H.: Praktische Erfahrungen über die zuckerige und einfache Harnruhr, Cor.-Bl. f. schweiz. Aertze **18**:393, 1888.

Engel, K.: Ueber Diabetes insipidus, Ztschr. f. klin. Med. **67**:112, 1909.

Eppinger, H.: Zur Pathologie und Therapie des menschlichen Oedems, Berlin, Julius Springer, 1917.

Erdheim, J.: Ueber Hypophysengangsgeschwülste und Hirncholesteatome, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **113**:537, 1904.

Farini, A.: Hypophyseal Opotherapy in Diabetes Insipidus, Gazz. d. osp. **34**: 1135, 1913; abstracted, Brit. M. J. **2**:76, 1913.

——and Ceccaroni, B.: Influenza degli estratti ipofisari sull' eliminazione dell' acido ippurico, Gazz. d. osp. **34**:879, 1913.

Findlayson, J.: Diabetes Insipidus with Great Enlargement of the Bladder, Glasgow M. J. **15**:17, 1881.

Findley, T., Jr.: Thyroid-Pituitary Relationship in Diabetes Insipidus, Ann. Int. Med. **11**:701, 1937.

——and Heinbecker, P.: Total Thyroidectomy for Human Diabetes Insipidus, Proc. Soc. Exper. Biol. & Med. **36**:448, 1937.

Fink, E. B.: Diabetes Insipidus: Clinical Review and Analysis of Necropsy Reports, Arch. Path. **6**:102 (July) 1928.

Finkelnburg, R.: Klinische und experimentelle Untersuchungen über Diabetes insipidus, Deutsches Arch. f. klin. Med. **91**:345, 1907.

Ueber das Konzentrationsvermögen der Niere bei Diabetes insipidus nach organischen Hirnerkrankungen, ibid. **100**:33, 1910.

Fisher, C., and Ingram, W. R.: Effect of Feeding of Thyroid or Salt and of Thyroidectomy on Fluid Exchange of Cats with Diabetes Insipidus, Arch. Int. Med. **58**:117 (July) 1936.

Effect of Interruption of Supraoptico-Hypophyseal Tracts on Antidiuretic, Pressor and Oxytocic Activity of the Posterior Lobe of the Hypophysis, Endocrinology **20**:762, 1936.

——Ingram, W. R., and Ranson, S. W.: Relation of the Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935.

Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

——Ingram, W. R.; Hare, W. K., and Ranson, S. W.: Degeneration of Supraoptico-Hypophyseal System in Diabetes Insipidus, Anat. Rec. **63**:29, 1935.

Fitz, R.: Case of Diabetes Insipidus, Arch. Int. Med. **14**:706 (Oct.) 1914.

Flandin, C.; Poumeau-Delille, G.; Puech, and Auzépy, P.: Diabète insipide et obésité avec vergetures par atteinte infundibulo-tubérienne d'origine ourlienne, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1244, 1935.

Forró, E., and Lendvai, J.: Ueberempfindlichkeit gegen Hypophysenhinterlappenextract in einem Falle von Diabetes insipidus, Wien. klin. Wchnschr. **49**:757, 1936.

Forschbach: Zur Frage des Konzentriervermögens der Niere beim Diabetes insipidus, Ztschr. f. klin. Med. **77**:153, 1913.

——and Weber: Beobachtungen über die Harn- und Salz- Ausscheidung im Diabetes insipidus, ibid. **73**:221, 1911.

Frank, E.: Ueber Beziehungen der Hypophyse zum Diabetes insipidus, Berl. klin. Wchnschr. **49**:393, 1912.

Futcher, T. B.: Diabetes insipidus, with Report of Five Cases, Johns Hopkins Hosp. Rep. **10**:197, 1901-1902.

Etiology and Treatment of Diabetes Insipidus, Ann. Int. Med. **5**:566, 1931.

Gänsslen, M., and Fritz: Diabetes insipidus, Klin. Wchnschr. **3**:22, 1924.

Gaupp, R.: Diabetes insipidus und Zwischenhirn, Klin. Wchnschr. **13**:1012, 1934.

Gayler: Ueber das Zustandekommen der Wachstumsstörungen bei Diabetes insipidus des Kindes, Monatschr. f. Kinderh. **21**:356, 1921.

Gee, S.: A Contribution to the History of Polydipsia, St. Barth. Hosp. Rep. **13**:79, 1877.

Gibson, R. B.; Magers, E. J., and Dulaney, H.: Blood Sugar Curves in Diabetes Insipidus and in Habitual and Experimental Excessive Water Drinking, Endocrinology **11**:341, 1927.

——and Martin, F. T.: Administration of a Pituitary Extract and Histamin in a Case of Diabetes Insipidus, Arch. Int. Med. **27**:351 (March) 1921.

Globus, J. H.: Teratoid Cyst of the Hypophysis, Arch. Neurol. & Psychiat. **9**:417 (April) 1923.

Gold, P.: Ueber Diabetes insipidus bei Meningitis tuberculosa, Dissert., Universität zu Zürich, 1935.

Gorke, H., and Deloch, E.: Ueber das Verhalten der Magen- und Darmfunktion beim Diabetes insipidus, Med. Klin. **17**:1146, 1921.

Grady, H. G., and Stewart, H. L.: Hand-Schüller-Christian's Disease and Tuberculosis, Arch. Path. **18**:699 (Nov.) 1934.

Graham, E. A.: Spinal Puncture in Diabetes Insipidus, J. A. M. A. **69**:1498 (Nov. 3) 1917.

Grassheim, K.: Über "primäre Oligurie," ihr Wesen und die Ursachen ihrer Entstehung, Ztschr. f. klin. Med. **110**:469, 1929.

Wasser- und Kochsalzstoffwechsel beeinflussende Stoffe im Liquor bei Erkrankungen des hypophysären Systems, Klin. Wchnschr. **11**:1257, 1932.

Greving, R.: Beitrag zur Innervation der Hypophyse, Klin. Wchnschr. **4**: 2181, 1925.

Griffith, J. P. C.: Xanthoma Tuberosum, with Early Jaundice and Diabetes Insipidus, Arch. Pediat. **39**:297, 1922.

Grosh, L. C., and Stifel, J. L.: Defects in Membranous Bones, Diabetes Insipidus, and Exophthalmus, Arch. Int. Med. **31**:76 (Jan.) 1923.

Grote, L. R.: Ueber die Funktion der Niere bei Diabetes insipidus, Deutsches Arch. f. klin. Med. **122**:223, 1917.

Hachen, D. S.: Studies in Renal Function and Metabolism in a Case of Diabetes Insipidus, Am. J. M. Sc. **165**:846, 1923.

Hagenbach, E.: Ein Fall von Diabetes insipidus, Jahrb. f. Kinderh. **19**:214, 1882.

Hall, G. W.: Diabetes Insipidus: Case Report Following Epidemic Encephalitis with Enormous Polyuria, Am. J. M. Sc. **165**:551, 1923.

Hand, A.: Defects of Membranous Bones, Exophthalmos and Polyuria in Childhood: Is It Dyspituitarism? Am. J. M. Sc. **162**:509, 1921.

Polyuria and Tuberculosis, Arch. Pediat. **10**:673, 1893.

von Hann, F.: Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, Frankfurt. Ztschr. f. Path. **21**:337, 1918.

Hanson, W. A.; Fowler, L. H., and Bell, E. T.: Case of Schüller-Christian's Disease Under Observation for Nine Years, Am. J. Cancer **25**:768, 1935.

Harmeier, J. W., and Finney, W. P.: Deformity from Fatty Atrophy in the Arm Occasioned by Injections of Pituitrin in Cases of Diabetes Insipidus, M. Clin. North America **13**:1533, 1930.

Harvey, A.: A Case of Diabetes Insipidus Permanently Cured by an Intercurrent Attack of Measles, Birmingham M. Rev. **31**:166, 1892.

Hatzieganu, J., and Hanganutziu, M.: Un nouveau traitement (protéinique) du diabète insipide, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:373, 1925.

Haushalter, P., and Lucien: Polyurie simple et tubercle de l'hypophyse, Rev. neurol. **12**:1, 1908.

Hausman, L., and Bromberg, W.: Diabetic Exophthalmic Dysostosis, Arch. Neurol. & Psychiat. **21**:1402 (June) 1929.

Haymann, K., and Fanconi: Zum Chemismus des Diabetes insipidus, Ztschr. f. d. ges. exper. Med. **51**:588, 1926.

Healy, J. W.: Diabetes Insipidus as a Manifestation of General Miliary Tuberculosis, Brit. J. Child. Dis. **32**:275, 1935.

Henschen, F.: Ueber Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose, Acta pædiat. (supp. 6) **12**:1, 1931.

Herrick, J. B.: Report of a Case of Diabetes Insipidus with Marked Reduction in the Amount of Urine Following Lumbar Puncture, Arch. Int. Med. **10**:1 (July) 1912.

Herring, P. T.: Histological Appearances of the Mammalian Pituitary Body, Quart. J. Exper. Physiol. **1**:161, 1908.

Herzenberg, H.: Die Skelettform der Niemann-Pickschen Krankheit, Virchows Arch. f. path. Anat. **269**:614, 1928.

Hijmans van den Bergh, A. A., and van Hasselt, J. A.: Tumor glandulae pinealis, sive epiphysis cerebri, Nederl. tijdschr. v. geneesk. **1**:1271, 1913.

Hirsch, O.: Rolle der Hypophyse und des Hypothalmus beim Diabetes insipidus (Beobachtungen am Patienten und Implantationen von tierischen und menschlichen Hypophysen), Wien. klin. Wchnschr. **50**:299, 1937.

——and Demel, R.: Ueber Implantation von tierscher und menschlicher Hypophyse bei Diabetes insipidus, ibid. **49**:523, 1936.

Von Hoesslin, R.: Tumor der Epiphysis cerebri: Diabetes insipidus: Oculomotoriuskernlähmung, München. med. Wchnschr. **43**:292, 1896.

Horrax, G., and Bailey, P.: Tumors of the Pineal Body, Arch. Neurol. & Psychiat. **13**:423 (April) 1925.

Horsfall, F. L., Jr., and Smith, W. R.: Schüller-Christian Syndrome: Lipoid-Granulomatosis with Defects in Bones, Exophthalmos, and Diabetes Insipidus, Quart. J. Med. **4**:37, 1935.

Houssay, B.: Pituitary Body and Polyuria, Endocrinology **2**:94, 1918.

Ingram, W. R.; Fisher, C., and Ranson, S. W.: Experimental Diabetes Insipidus in the Monkey, Arch. Int. Med. **57**:1067 (June) 1936.

Iversen, P.; Jacobsen, E., and Bing, J.: Nierenfunktionsuntersuchungen bei Diabetes insipidus: Pituinwirkung—Tages- und Nachtfiltration—Adrenalinwirkung, Arch. f. exper. Path. u. Pharmakol. **174**:69, 1933.

Jaensch, P. A.: Seltene Augenveränderungen bei Schüller-Christianscher Krankheit, Klin. Monatsbl. f. Augenh. **92**:158, 1934.

Jánossy, J.: Ueber die Wirkung der intrazisternös verabreichten Hypophysenpräparate, Ztschr. f. klin. Med. **103**:715, 1926.

Janssen, S.: Ueber die Bahnen der zentralen Wasserregulation und der Hypophysenantidiurese, Klin. Wchnschr. **7**:1680, 1928.

Janzen, E., and Broekman, J.: A Case of Hereditary Diabetes Insipidus, Nederl. tijdschr. v. geneesk. (pt. 1) **65**:2519, 1921.

Jewett, D. B.: Hypophyseal Disease as Related to Diabetes Insipidus, with Report of Two Cases, M. Rec. **85**:242, 1914.

Just, G.: Ein Wort zu Weils Diabetes insipidus-Stammbaum, Arch. f. Rassen- u. Gesellsch.-Biol. **16**:312, 1925.

Kahler, O.: Ueber experimentelle Erzeugung von dauernder Polyurie, Verhandl. d. Cong. f. inn. Med. **5**:323, 1886.

Kahn, B. S.: Use of Amidopyrine in a Case of Diabetes Insipidus, J. A. M. A. **100**:1593 (May 20) 1933.

Kamm, O.; Aldrich, T. B.; Grote, I. W.; Rowe, L. W., and Bugbee, E. P.: Active Principles of the Posterior Lobe of the Pituitary Gland, J. Am. Chem. Soc. **50**:573, 1928.

Kay, M. B.: Hypopituitarism (Fröhlich Type) in an Infant Nine Months Old, Endocrinology **5**:325, 1921.

Keller, A. D.: Hypophyseal Thyrotropic Mechanism Essential for the Occurrence of Diabetes Insipidus in Its Maximal Form, Proc. Soc. Exper. Biol. & Med. **36**:787, 1937.

Kennaway, E. L., and Mottram, J. C.: Observations upon Two Cases of Diabetes Insipidus, with an Account of the Literature Relating to an Association Between the Pituitary Gland and This Disease, Quart. J. Med. **12**:225, 1919.

Knöpfelmacher: Diabetes insipidus bei Kindern, abstracted, Zentralbl. f. inn. Med. **26**:326, 1905.

Koral, cited by Eichhorn.

Külz, in Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1887-1893, vol. 13, p. 1.

Kyrklund, R.: Beitrag zu einem seltenen Symptomenkomplex (Schädelerweichungen, Exophthalmus, Dystrophia adip. genit., Diabetes insipidus), Ztschr. f. Kinderh. **41**:56, 1926.

Labbé, M., and Dreyfus, G.: Diabète insipide et trouble de la glycorégulation, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:142, 1932.

——Boulin, R.; Krebs; Justin-Besançon, L., and Uhry, P.: Deux observations de potomanes, ibid. **47**:1072, 1931.

——Boulin, R.; Justin-Besançon, L., and Uhry, P.: Présentation d'une potomane, ibid. **47**:1151, 1931.

Lacombe, L. U.: De la polydipsie, Thesis, Paris, no. 99, vol. 375, 1841.

Lacy, C. S.: Three Cases of Diabetes Insipidus Successfully Treated by Ergot, M. News **42**:9, 1883.

Laffon, M.: Tumor suprasillar: Combinación de diabetes insipida y sindrome de Fröhlich, Arch. españ. de pediat. **17**:64, 1933.

de Lange, C.: Pseudodiabetes Insipidus in Relation to Renal Dwarfism, Nederl. tijdschr. v. geneesk. **77**:4652, 1933.

Ueber erblichen Diabetes insipidus, Jahrb. f. Kinderh. **145**:1, 1935.

Lauritzen, M.: On Hereditary Diabetes Insipidus, Hospitalstid. **1**:353, 392, 423 and 451, 1893.

Lenk, R.: Akute Leukämie und Diabetes insipidus bei Status thymicohypoplasticus, Wien. klin. Wchnschr. **24**:1130, 1911.

Lereboullet, P.: La technique de l'apothérapie hypophysaire chez l'enfant, Arch. de méd. d. enf. **39**:442, 1936.

Leschke, E.: Beiträge zur klinischen Pathologie des Zwischenhirns: I. Klinische und experimentelle Untersuchungen über Diabetes insipidus, seine Beziehungen zur Hypophyse und zum Zwischenhirn, Ztschr. f. klin. Med. **87**:201, 1919.

Lesné, E.; Hutinel, J.; Marquézy, R. A., and Benoist: Diabète insipide chez un enfant: Inefficacité du traitement par injections d'extrait hypophysaire; action remarquable des prises de poudre par voie nasale, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:70, 1929.

——Launay, C., and Sée, G.: Diabète insipide au cours d'une maladie de Besnier-Bœck, Bull. Soc. franç. de dermat. et syph. (Réunion dermat.) **42**:1671, 1935.

——Liévre, J. A., and Boquien, Y.: Xanthomatose crâniohypophysaire (Maladie de Schüller-Christian), Arch. de méd. d. enf. **35**:598, 1932.

Levinson, A.: Diabetes Insipidus, Am. J. Dis. Child. **32**:154 (July) 1926.

Levit, S. G., and Pessikova, L. N.: Genetics of Diabetes Insipidus and Its Bearing on the Problem of Dominance in Man, J. Hered. **27**:445, 1936.

Lichtwitz, L.: Die Konzentrationsarbeit der Niere, Arch. f. exper. Path. u. Pharmakol. **65**:128, 1911.

——and Stromeyer, F.: Untersuchungen über die Nierenfunktion: Die Funktion der Niere im Diabetes insipidus, Deutsches Arch. f. klin. Med. **116**:127, 1914.

Lichty, D. E.: Lipoids and Lipoid Diseases: Xanthomatosis (Schüller-Christian's Type), Arch. Int. Med. **53**:379 (March) 1934.

Liebmann, A.: Ueber Diabetes insipidus bei Kindern, Berlin, O. Francke, 1888.

McConnell, A. A.: Case of Diabetes Insipidus Influenced by Partial Thyroidectomy, Irish J. M. Sc., 1936, p. 742.

McCrae, T., and Weiss, E.: Laurence-Biedl Syndrome: Adiposity, Retinitis Pigmentosa, Mental Deficiency, and Polydactylism, M. Clin. North America **14**:825, 1931.

McIlraith, C. H.: Notes on Some Cases of Diabetes Insipidus with Marked Family and Hereditary Tendencies, Lancet **2**:767, 1892.

McKinney, J. M.: The Laurence-Biedl Syndrome, J. Nerv. & Ment. Dis. **74**:50, 1931.

Madigan, J. J., and Moore, T. V.: Dystrophia Adiposogenitalis (Fröhlich's Syndrome), J. A. M. A. **70**:669 (March 9) 1918.

Mahoney, W.: Die chirurgische Beeinflussung des Diabetes insipidus und Diabetes mellitus, Arch. f. klin. Chir. **186**:191, 1936.

——and Sheehan, D.: Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs, Am. J. Physiol. **112**:250, 1935.

Marañon, G.: Diabetes Insipidus as a Hypopituitary Syndrome, Endocrinology **5**:159, 1921.

——and Pintos, G.: Lésion traumatique pure de l'hypophyse: Syndrome adiposo-génital et diabète insipide, Nouv. iconog. de la Salpêtrière **28**:125, 1910.

Marinesco, G.: Deux cas de polyurie familiale dite essentielle, Compt. rend. Soc. de biol. **2**:41, 1895.

——Sager, O., and Soru, E.: Recherches sur le $p_H$ intratissulaire dans le diabète insipide, ibid. **103**:171, 1930.

Martin, P., and Cushing, H.: Primary Gliomas of Chiasm and Optic Nerves in Their Intracranial Portion, Arch. Ophth. **52**:209, 1923.

Martinez, O., and Navarron: Zwei Fälle der familiären Form des idiopathischen Diabetes insipidus mit Hypophysenbehandlung, Rev. d. Circ. med. de Córdoba **10**:78, 1922; cited by Chester and Spiegel.

Meijers, E. J.: Diabetes Insipidus in Children, Nederl. tijdschr. v. geneesk. **2**: 5336, 1929.

Melli, G.: Il morbo di Schüller-Christian, Policlinico (sez. med.) **42**:449 and 509, 1935.

Mensi, E.: Diabete insipido infantile, Minerva med. **2**:813, 1922.

Merritt, K. K., and Paige, B. H.: Xanthomatosis (Schüller-Christian Syndrome): Report of a Case with Necropsy, Am. J. Dis. Child. **46**:1368 (Dec.) 1933.

Meyer, E.: Ueber Diabetes insipidus und andere Polyurien, Deutsches Arch. f. klin. Med. **83**:1, 1905.

Bemerkungen zu der Arbeit von Forschbach und Weber: Beobachtungen über die Harn- und Salzausscheidung im Diabetes insipidus, Ztschr. f. klin. Med. **74**:352, 1912.

——and Meyer-Bisch, R.: Weitere Mitteilung über die Pathogenese des Diabetes insipidus, Klin. Wchnschr. **3**:1796, 1924.

Meyer-Nobel, K.: Beeinflussung eines Falles von Diabetes insipidus durch Corpus-luteum-Extrakt, München. med. Wchnschr. **77**:1844, 1930.

Moffett, R. D.: Craniopharyngeal Pouch Cyst Arising from Pituitary Body: Operation with Recovery, Am. J. Dis. Child. **32**:89 (July) 1926.

——and Greenberger, M.: Diabetes Insipidus in Children, M. Rec. **92**:487, 1917.

Molitor, H., and Pick, E.: Ueber zentrale Regulation des Wasserwechsels: I. Der Einfluss des Grosshirns auf die Pituitrinhemmung, Arch. f. exper. Path. Pharmakol. **107**:180, 1925.

Ueber zentrale Regulation des Wasserwechsels: II. Ueber den zentralen Angriffspunkt der Diureschemmung durch Hypophysenextrakte, ibid. **112**: 113, 1926.

Mosler, F.: Neuropathische Entstehung der einfachen Harnruhr (Hydrurie) durch Meningitis cerebrospinalis epidemica, durch Trauma, durch Syphilis, Virchows Arch. f. path. Anat. **58**:44, 1873.

Murrell, W.: On a Case of Diabetes Insipidus Treated by (1) Belladonna and (2) Ergot, Brit. M. J. **1**:8, 1876.

Newmark, L.: Case of Infundibular Tumor in a Child Causing Diabetes Insipidus with Tolerance of Alcohol, Arch. Int. Med. **19**:550 (April) 1917.

Nobécourt, P., and Ducas, P.: Diabetes Insipidus, in Nobécourt, P., and Babonneix, L.: Traité de médecine des enfants, Paris, Masson & Cie, 1934, vol. 1, p. 305.

Nonne, M.: Hypophysiserkrankungen, München. med. Wchnschr. **63**:835, 1916. Syphilis und Nervensystem, Berlin, S. Karger, 1915, p. 241.

Oehme, C., and Oehme, M.: Zur Lehre vom Diabetes insipidus; Nach experimentellen Untersuchungen, Deutsches Arch. f. klin. Med. **127**:261, 1918.

Orsi, F.: Cúriosità cliniche, sei individui d'una stessa familia colpiti da idruria, Gazz. med. tal. lomb. **3**:352, 1881.

Pacella, O.: Diabete insipido infantile (Ricerche sulla glicemia), Gazz. internaz. med.-chir. **39**:21, 1931.

Pain, G.: Notes à propos de quelques observations de polyurie chronique, Thesis, Paris, no. 427, 1879, p. 19.

Pashkoff, B. M., and Smelov, N. S.: Diabetes Insipidus and Acromegaly in Congenital and Acquired Syphilis, Sovet. klin. **16**:23, 1931.

Peterman, M. G.: Diabetes Insipidus: Case Report, Am. J. Dis. Child. **38**:1335 (Dec.) 1929.

Peters, J. P.: Body Water, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

Pincherle, M., and Magni, L.: Note cliniche, anatomiche e di patogenesi sul diabete insipido giovanile, Arch. di pat. e clin. med. **3**:261, 1924.

Pines, I. L.: Ueber die Innervation der Hypophysis cerebri, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:123, 1925.

Ueber die Innervation der Hypophysis cerebri, ibid. **107**:507, 1927.

Popa, G. T., and Fielding, U.: Portal Circulation from Pituitary to Hypothalamic Region, J. Anat. **65**:88, 1930.

Vascular Link Between Pituitary and Hypothalamus, Lancet **2**:238, 1930.

Popoff, A.: Diabetes Insipidus in Childhood, Med. Obozr. **40**:3, 1903; abstracted, Centralbl. f. Kinderh. **9**:344, 1904.

Pusey, W. A., and Johnstone, O. P.: Case of Xanthoma Diabeticorum and Lipoma Multiplex and a Case of Xanthoma Approaching the Diabetic Type with Diabetes Insipidus, J. Cutan. Dis. **26**:552, 1908.

Raab, W.: Das Hypophysen-Zwischenhirnsystem und seine Störungen, Ergebn. d. inn. Med. u. Kinderh. **51**:125, 1936.

Ramón y Cajal, S.: Histologie du système nerveux de l'homme et des vertébrés, translated by L. Azoulay, Paris, A. Maloine, 1909.

Ranson, S. W.: Some Functions of the Hypothalamus, Bull. New York Acad. Med. **13**:241, 1937.

Rassulev, J. A.: Ueber Diabetes insipidus bei Pellagra, Arch. f. Schiffs- u. Tropen. Hyg. **36**:481, 1932.

Reichardt, M.: Der Diabetes insipidus, Symptom einer Geisteskrankheit? Arb. a. d. psychiat. Klin. zu Würzburg, 1908, no. 2, p. 49.

Reilly, W. A., and Lisser, H.: Laurence-Moon-Biedl Syndrome, Endocrinology **16**:337, 1932.

Reith: Polydipsia: Treatment by Large Doses of Valerian; Improvement: Clinical Remarks, M. Times & Gaz. **1**:309, 1866.

Richter, C. P.: Experimental Diabetes Insipidus: Its Relation to Anterior and Posterior Lobes of Hypophysis, Am. J. Physiol. **110**:439, 1934.

Primacy of Polyuria in Diabetes Insipidus, ibid. **112**:481, 1935.

——and Eckert, J. F.: Further Evidence for Primacy of Polyuria in Diabetes Insipidus, ibid. **113**:578, 1935.

Rietschel, H.: Ueber Lipoidgranulomatose oder allgemeine granulomatöse Xanthomatose (Hand-Schüller-Christiansche Krankheit), Ztschr. f. Kinderh. **54**:65, 1932.

Rochlin, M.: Diabetes in Children, abstracted, Zentralbl. f. Kinderh. **9**:343, 1903.

Roehm, H. R.: Postvaccinal Encephalitis Associated with Diabetes Insipidus, Am. J. Dis. Child. **44**:1293 (Dec.) 1932.

Römer, C.: Die Beziehungen zwischen der Funktion der Hypophysis cerebri und dem Diabetes insipidus, Deutsche med. Wchnschr. **40**:108, 1914.

Rosenbloom, J.: Control of Polyuria in a Case of Diabetes Insipidus by Means of Hypophyseal Extract, J. A. M. A. **70**:1292 (May 4) 1918.

Rothmann, H.: Zur Behandlung des Diabetes insipidus mit Hodenextrakt, Med. Klin. **21**:1535, 1925.

Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System: Correlation of Unidentified Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome), Arch. Int. Med. **42**:611 (Nov.) 1928.

Rowntree, L. G.: Diabetes Insipidus, J. A. M. A. **83**:399 (Aug. 9) 1924.

Differential Diagnosis of Polyuria, with Special Reference to Diabetes Insipidus, M. Clin. North America **5**:439, 1921.

Sajous, C. E. de M.: Hypophyseobasal Area in Its Relation to the Pathogenesis and Treatment of Diabetes Insipidus and Polyuria, Am. J. M. Sc. **167**:679, 1924.

Salmi, T.: Diabetes Insipidus Complicating Chickenpox, Duodecim **52**:304, 1936.

Salmonsen, L.: Beitrag zur Frage der Pathogenese des Diabetes insipidus, Acta pædiat. **3**:261, 1924.

Sasse, C.: Ein neurer Fall von hereditärem Diabetes insipidus, Thesis, Bonn, J. Bach Wwe., 1893.

Sato, G.: Ueber die Beziehungen des Diabetes insipidus zum Hypophysenhinterlappen und zum Tuber cinereum, Arch. f. exper. Path. u. Pharmakol. **131**: 45, 1928.

Scharrer, E., and Gaupp, R., Jr.: Bemerkungen und Versuche zur Frage der Beziehungen zwischen Schilddrüse und Zwischenhirndrüse, Klin. Wchnschr. **14**:1651, 1935.

Scherf, D.: Pyramidon beim Diabetes insipidus, Wien. Arch. f. inn. Med. **22**: 457, 1932.

Schube, P. G.: Encephalography in Abnormal Mental States with Diabetes Insipidus, J. Nerv. & Ment. Dis. **78**:453, 1933.

Schüller, A.: Ueber eigenartige Schädeldefekte im Jugendalter, Fortschr. a. d. Geb. d. Röntgenstrahlen **23**:12, 1915.

Schulmann, E., and Lichtwitz, A.: La syphilis de l'hypophyse, Rev. franç. de dermat. et de vénéréol. **1**:680, 1925.

Schulz, A.; Wermbter, F., and Puhl, H.: Eigentümliche granulomartige Systemerkrankungen des hämatopoetischen Apparates (Hyperplasie des retikuloendothelialen Apparates), Virchows Arch. f. path. Anat. **252**:519, 1924.

Secrétan: Diabète insipide et pituitrine, Arch. de méd. d. enf. **26**:502, 1923.

Senator, H.: Ueber die Beziehungen zwischen Diabetes mellitus und insipidus. Deutsche med. Wchnschr. **23**:385, 1897.

Sheldon, J. H.: Diabetes Insipidus Occurring in a Case of Lymphatic Leukaemia of the Aleukaemic Type, Lancet **1**:489, 1927.

Signorelli, E.: Diabete insipido fra gli esiti dell' encefalite epidemica, Arch. di pat. e clin. med. **2**:89, 1923.

Silvestri, T.: Diabete insipido e pubertà, Riforma med. **37**:412, 1921.

Simmonds, M.: Ueber sekundäre Geschwülste des Hirnanhangs und ihre Beziehungen zum Diabetes insipidus, München. med. Wchnschr. **61**:180, 1914.

Snell, A. M.: Water Intoxication in Cases of Diabetes Insipidus, M. Clin. North America **12**:1667, 1929.

——and Rowntree, L. G.: Clinical Manifestations of Water Intoxication in a Case of Severe Diabetes Insipidus, with Some Notes on Disturbances of Blood Composition and Vasomotor Mechanism, Endocrinology **11**:209, 1927.

Sosman, M. C.: Xanthomatosis (Schüller's Disease; Christian's Syndrome): Report of Three Cases Treated with Roentgen Rays, Am. J. Roentgenol. **23**:581, 1930.

Xanthomatosis (Schüller-Christian's Disease; Lipoid Histiocytosis), J. A. M. A. **98**:110 (Jan. 9) 1932.

Souques; Alajouanine, and Lermoyez, J.: Sur un cas de diabète insipide et sur les actions des extraits de lobe postérieur d'hypophyse, Rev. neurol. **29**:766, 1922.

Sparrow, T. D., and Fetner, L. M.: Xanthomatosis, J. A. M. A. **99**:2176 (Dec. 24) 1932.

Spohn, H.: Diabetes Insipidus, Am. J. Dis. Child. **36**:865 (Oct.) 1928.

Starling, E. H.: Secretion of the Urine as Studied on the Isolated Kidney, Proc. Roy. Soc., London, s.B **97**:321, 1925.

Stern, R.: Ueber traumatische Entstehung innerer Krankheiten, Jena, Gustav Fischer, 1907-1913.

Strauch, A.: Hypophysial Dystrophy in Hydrocephalus, J. A. M. A. **72**:1731 (June 14) 1919.

Strauss, L.: Uebergang eines Falles von Diabetes insipidus in Myxödem, Deutsche med. Wchnschr. **46**:939, 1920.

Strubell, A.: Ueber Diabetes insipidus, Deutsches Arch. f. klin. Med. **62**:89, 1898.

Sugimoto, C.: Diabetes Insipidus with Familial Tendency, J. Pediat. (Tokyo), 1931, no. 376, p. 1235.

Sulzberger, M. B.: Pituitary Hormone Intermedin as Active Antidiuretic in the Treatment of Diabetes Insipidus: Preliminary Report, J. A. M. A. **100**: 1928 (June 17) 1933.

Tallqvist, T. W.: Untersuchungen über einen Fall von Diabetes insipidus, Ztschr. f. klin. Med. **49**:181, 1903.

Tate, B. C.: Cutaneous Xanthomata Associated with Intermittent Diabetes Insipidus: High Blood-Fat and Normal Blood Cholesterol, Proc. Roy. Soc. Med. **26**:1546, 1933.

Thompson, C. Q.; Keegan, J. J., and Dunn, A. D.: Defects of Membranous Bones, Exophthalmos and Diabetes Insipidus, Arch. Int. Med. **36**:650 (Nov.) 1925.

Thompson, W. H.; Johnson, R. M., and McQuarrie, I.: Diabetes Insipidus: A Study of the Water and Mineral Exchanges, Am. J. Dis. Child. **46**:930 (Oct.) 1933.

Tillgren, J.: Diabetes Insipidus as a Symptom of Schaumann's Disease, Brit. J. Dermat. **47**:223, 1935.

Touraine, A.; Golé, L., and Bernou: Diabète insipide et syndrome adiposo-génital chez une hérédo-syphilitique (Recherches interférométriques), Bull. Soc. franç. de dermat. et syph. **41**:745, 1934.

Trendelenburg, P.: Anteil der Hypophyse und des Hypothalamus am experimentellen Diabetes insipidus, Klin. Wchnschr. **7**:1679, 1928.

Troisier, J.: Action antipolyurique des hautes doses de folliculine dans le diabète insipide de l'homme, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1451, 1932.

Trousseau, A.: Lectures on Clinical Medicine Delivered at the Hôtel-Dieu, Paris, ed. 3, translanted by J. R. Cormack, London, New Sydenham Society, 1870-1872, p. 528.

Tucker, J.: Immediate Recovery from Early Diabetes Insipidus After Lumbar Puncture, Am. J. M. Sc. **163**:668, 1922.

Turner, H. H.: Diabetes Insipidus: Treatment with Intermedin and Pitmelanin, Endocrinology **19**:275, 1935.

Turner, J. H.: Diabetes Insipidus: Report of a Case in a Child, Arch. Pediat. **45**: 433, 1928.

Vámos, G.: A New Case of Diabetes Insipidus, Pest. med.-chir. Presse **26**:793, 1890; abstracted, Jahrb. f. Kinderh. **34**:295, 1892.

Veil, W. H.: Die Beziehungen der experimentellen Piqure-Polyurie zum Diabetes insipidus, Deutsche med. Wchnschr. **46**:558, 1920.

Physiologie und Pathologie des Wasserhaushaltes, Ergebn. d. inn. Med. u. Kinderh. **23**:648, 1923.

von den Velden, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berl. klin. Wchnschr. **50**:2083, 1913.

Verney, E. B.: Goulstonian Lectures on Polyuria; Polyuria Associated with Pituitary Dysfunction, Lancet **1**:539, 1929.

Versmann, H.: Ueber Syphilis als Causalmoment des Diabetes insipidus, Würzburg, Becker, 1882.

Vierordt, H.: Ein exquisiter Fall von Diabetes insipidus im Kindesalter, Jahrb. f. Kinderh. **28**:95, 1888.

Wachsmuth, H.: Ein Fall von Diabetes insipidus, Virchows Arch. f. path. Anat. **26**:318, 1863.

Warkany, J.; Frauenberger, G. S., and Mitchell, A. G.: Heredofamilial Deviations: Laurence-Moon-Biedl Syndrome, Am. J. Dis. Child. **53**:455 (Feb.) 1937.

Weber, F. P.: Diabetes Insipidus in a Boy with Positive Wassermann's Reaction, Brit. J. Child. Dis. **9**:211, 1912.

Weil, Adolf: Ueber die hereditäre Form des Diabetes insipidus, Virchows Arch. f. path. Anat. **95**:70, 1884.

Weil, Alfred: Ueber die hereditäre Form des Diabetes insipidus, Deutsches Arch. f. klin. Med. **93**:180, 1908.

Weir, J. F.; Larson, E. E., and Rowntree, L. G.: Studies in Diabetes Insipidus, Water Balance, and Water Intoxication, Arch. Int. Med. **29**:306 (March) 1922.

Weiss, E.: Ueber die Reaktion des kindlichen Diabetes insipidus auf Hypophysenpräparate, Monatschr. f. Kinderh. **40**:428, 1928.

Wentzler, E.: Ein Fall von Carcinom der Hypophyse bei 9 jährigem Knaben, Monatschr. f. Kinderh. **69**:86, 1937.

Whitehead, R. W., and Darley, W.: Case of Diabetes Insipidus Occurring as a Sequel to Epidemic Encephalitis, Endocrinology **15**:286, 1931.

Whittle, 1867, cited by Eichhorn.

Wortis, S. B.; Wolf, A., and Dyke, C. G.: Xanthomatosis and Syndrome of Diabetic Exophthalmic Dysostosis, Am. J. Dis. Child. **51**:353 (Feb.) 1936.

Zenker, F.: Diabetes insipidus und Trauma, Weissenfels, W. Nitsche, 1919.

# News and Comment

## GENERAL

**Child Health Day, Monday, May 1, 1939.**—The May Day celebration is sponsored, as usual, by the Children's Bureau of the United States Department of Labor. The slogan is "The health of the child is the power of the nation." The object is to bring to the attention of each community the importance to the child's health, development and well-being throughout life of proper food, rest, exercise, medical care and protection against disease; the ways of informing parents and others how child health may be safeguarded, and the means whereby such safeguards may be made available for all children.

**American Board of Pediatrics.**—The American Board of Pediatrics will hold examinations on November 14 and 15, in Cincinnati, preceding the annual meeting of the American Academy of Pediatrics. Appointments for this examination must be made before July 14, 1939.

## UNIVERSITY NEWS

**University of Pennsylvania.**—Dr. Joseph Stokes Jr. will assume the chair of pediatrics at the Medical School of the University of Pennsylvania on the retirement of Prof. John C. Gittings at the end of the school year.

## DEATHS

Dr. Harry C. Berger, a pediatrician of Kansas City, Mo., died of coronary occlusion on March 5, at the age of 49.

Dr. Étienne Leenhardt, professor of pediatrics of the Faculty of Medicine of Montpellier, France, died recently at the age of 63 years.

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## CORRECTION

In the article by Dr. Adrien Bleyer, entitled "Role of Advanced Maternal Age in Causing Mongolism: A Study of 2,822 Cases," which appeared in the January 1938 issue (Am. J. Dis. Child. **55**:79, 1938), there were a few errors in figures:

In the table on page 82, entitled "A Comparison of Births of Mongoloid Imbeciles Occurring in Nine Quinquenniums with Births Occurring in the General Population of the United States in Similar Periods," the fifth, sixth and seventh percentages should have been 5.1, 3.5 and 0.3 (instead of 0.9, 0.3 and 0.03).

Similarly, in the ratios on the following page, "5 to 1" should replace "25 to 1"; "7.5 to 1" should replace "75 to 1," and "12.5 to 1" should replace "125 to 1." Like substitutions should be made in the conclusions on the last page.

Dr. Lucy Porter Sutton, who died on December 23 (Am. J. Dis. Child. **57**:169 [Jan.] 1939), was assistant professor of pediatrics in the New York University College of Medicine for seven or eight years. She was especially well known for the development of the treatment of chorea by induced fever.

# Obituaries

## PERCIVAL J. EATON

1862—1939

Dr. Percival J. Eaton, who was born in Malden, Mass., on Feb. 13, 1862, recently died at his home in Provincetown, Mass. He received his M.D. degree from Harvard University in 1888, and afterward studied in Vienna, London, Edinburgh and Dublin.

Dr. Eaton was for many years a leading pediatrician in Pittsburgh, where he helped to develop the Children's Hospital and the department of pediatrics in the University of Pittsburgh. He was on the staffs of St. Margaret's Memorial Hospital, West Pennsylvania Hospital, the Columbia Hospital and the Children's Hospital. In 1904 he was elected to membership in the American Pediatric Society.

He was also interested in art, being for thirty years one of the directors of the Pittsburgh Art Society and for nine years its president. He was a charming conversationalist and a most kindly gentleman. His death removes one of the older and one of the most beloved figures in pediatrics in the United States.

# Abstracts from Current Literature

## Anatomy and Physiology

TWO CASES OF PERSISTENT LEFT SUPERIOR VENA CAVA IN MAN. J. W. PAPEZ, Anat. Rec. **70**:191 (Jan. 25) 1938.

Papez describes 2 cases of persistence of a left common cardinal vein emptying into the coronary sinus. In the first case the venae cavae on both sides were of equal size; in the second the left was the smaller.

SNELLING, Toronto, Canada.

A CASE OF LEFT SUPERIOR VENA CAVA WITHOUT A CORRESPONDING VESSEL ON THE RIGHT SIDE. W. J. ATWELL and P. ZOLTOWSKI, Anat. Rec. **70**:525 (April 25) 1938.

The authors describe the specimen and refer to 18 other authentic reports.

SNELLING, Toronto, Canada.

## Biochemistry; Bacteriology, and Pathology

FURTHER OBSERVATIONS ON BACTERIOPHAGE ACTION IN THE PRESENCE OF BLOOD. W. J. MACNEAL, M. A. MCRAE and R. A. COLMERS, J. Infect. Dis. **63**:25 (July-Aug.) 1938.

Exposure of susceptible pathogenic bacteria to a potent bacteriophage for a few minutes in a watery medium renders these bacteria much more susceptible to phagocytosis by living leukocytes. This opsonic effect of bacteriophage is also exerted in the presence of blood serum in the test tube and can be demonstrated in the blood of living animals during the first hour after intravenous injection of the bacteriophage. The opsonic effect is evidently one of the important immediate favorable influences of the bacteriophage when it is introduced into the infected patient.

TOOMEY, Cleveland.

ON THE SEROLOGICAL RESPONSE FOLLOWING THE USE OF ORAL TYPHOID VACCINE. H. H. HENGSTENBERG, J. Med. **19**:131 (May) 1938.

The agglutinin response to orally administered typhoid vaccine as determined in 197 persons six weeks after vaccination compared favorably with that developing in persons vaccinated hypodermically with a similar vaccine.

NELSON, Cincinnati.

"ACID" PHOSPHATASE ACTIVITY OF THE SERUM OF NORMAL HUMAN SUBJECTS. A. B. GUTMAN and E. B. GUTMAN, Proc. Soc. Exper. Biol. & Med. **38**:470 (May) 1938.

The blood serum of human subjects contains a phosphatase which is active on the acid side of neutrality. This "acid" phosphatase of normal serum has a broad range of optimal activity from about $p_H$ — 4.0 to $p_H$ — 6.5. The characteristics of this enzyme suggest that it is best classified as phosphomonoesterase $A_2$.

HANSEN, Minneapolis.

INFLUENCE OF KETENE ON THE POTENCY OF ANTIPNEUMOCOCCUS SERUM. J. T. TAMURA and M. J. BOYD, Proc. Soc. Exper. Biol. & Med. **38**:909 (June) 1938.

Ketene ($H_2C:CO$) bubbled through antipneumococcus horse serum does not change the protective antibody. In a prior article (*Proc. Soc. Exper. Biol. & Med.* **38**:184, 1938) the authors showed that administration of ketene-treated antibrucella horse serum did not induce an anaphylactic shock in animals sensitized to the original antiserum.

HANSEN, Minneapolis.

## Metabolism; Infant Feeding; Milk and Other Foods

STUDIES IN ABSORPTION OF UNDIGESTED PROTEIN IN HUMAN BEINGS: VII. ABSORPTION OF PROTEIN INTRODUCED BY TUBE INTO THE DUODENUM. I. GRAY and M. WALZER, Am. J. Digest. Dis. **5**:345 (Aug.) 1938.

The method of determining the rate of absorption was as follows: Peanut was excluded from the subject's diet for twenty-four hours preceding the test, which consisted in introducing intracutaneously into the forearm 0.5 cc. of a 1:10 dilution of the sensitizing serum (this serum was obtained from a patient who manifested a marked reaction to an intracutaneous test with peanut extract in a high dilution and who was extremely sensitive clinically to this food). On the morning after this passive local cutaneous sensitization, the subject was given the peanut test meal on an empty stomach. The meal consisted of a milk made by dissolving 10 Gm. of raw ground peanuts in 30 cc. of water with sugar and cloves added for taste. The entrance of unaltered protein (peanut) into the circulation was marked by the onset of a reaction at the sensitized cutaneous site. Pruritis was usually the first symptom noted. Erythema and wheal formation followed rapidly. The absorption time was the interval between the consumption of the test meal and the first objective sign at the sensitized site, namely, the erythema or the wheal. For the administration of the test meal in the present study, the duodenal tube was passed on a fasting stomach and the position of the buchet was localized with the aid of the fluoroscope. When it was visualized in the duodenum and bile was obtained on aspiration, the peanut meal was injected through the tube.

Gastric acidity was determined by fractional gastric analysis or by a Boas test meal.

Fourteen subjects were tested by both methods (oral and duodenal), the same serum being used with each method. Only a few days elapsed between the oral and the duodenal testing of each patient.

The authors found that (1) after the intraduodenal administration of a peanut test meal the rate of absorption of the unaltered peanut protein was more rapid by several minutes than the rate following oral consumption; (2) the rate of absorption from the duodenum in patients with gastric hyperacidity is not as rapid as the rate in persons with normal gastric acidity, and (3) the rate of absorption from the duodenum in patients with gastric hypoacidity is more rapid than that in persons with normal gastric acidity.

MORRISON, Savannah, Ga.

AN IMPROVED SANITARY CAP FOR NURSING BOTTLES. OSCAR J. KAHN, Arch. Pediat. **55**:218 (April) 1938.

The cap consists of a square of cellophane held in place below the lip of the bottle by a collar of cardboard.

ORR, Buffalo.

A CASE OF NUTRITIONAL EDEMA. H. LOWENBURG SR. and A. B. MILLER, Arch. Pediat. **55**:297 (May) 1938.

A case is reported.

ORR, Buffalo.

TRANSFERS OF WATER AND SOLUTES IN THE BODY. J. P. PETERS, Bull. New York Acad. Med. **14**:299 (June) 1938.

This is a comprehensive consideration of water metabolism, including its chemical and physiologic phases as they pertain to clinical activity.

JAHR, Omaha.

USE OF CAMPHOR IN OIL TO CHECK LACTATION. E. C. SMITH, New Orleans M. & S. J. **91**:127 (Sept.) 1938.

Smith reports the results of hypodermic injections of camphor in oil to check lactation in 115 cases. The injection dose was 3 grains (0.2 Gm.), and all injections were given intramuscularly. On the first two days a dose was injected both morning and night. After the second day a dose was injected once daily. The total number of injections varied from one to twelve, with an average of five. Eight to twelve hours after beginning treatment regressive changes were noted. The nonlactating period was reached in from two to four days instead of the usual four to six days. There were no unfavorable reactions.

Fifteen patients with polygalactia were treated with one or two injections. A satisfactory reduction of flow occurred without cessation and with no apparent effect on the infant.

The method is recommended as most effective for reducing or completely suppressing lactation.

BERKLEY, Los Angeles.

UNRECOGNIZED DISORDERS FREQUENTLY OCCURRING AMONG INFANTS AND CHILDREN FROM THE ILL EFFECTS OF MILK. W. A. MCGEE, South. M. J. **31**:1016 (Sept.) 1938.

McGee discusses allergy to milk, which very commonly occurs in young infants and children. He points out that a history of the feeding is far more important than skin tests in determining whether an infant is allergic. He recommends, however, that direct cutaneous and intracutaneous tests should be made. All positive reactions to these tests should be correlated clinically as far as possible in order to eliminate the main etiologic factors.

He believes that sensitivity to milk is extremely common among infants and is probably one of the main etiologic factors in allergic reactions.

SCHLUTZ, Chicago.

RELATION BETWEEN THE IODINE OF THE BLOOD AND THE BASAL METABOLISM IN CHILDREN. G. MACCIOTTA, Riv. di clin. pediat. **36**:425 (May) 1938.

Observations on 18 children between 1½ and 13 years of age showed that the percentage of iodine in the blood was not regularly proportional to the basal metabolism.

HIGGINS, Boston.

FROZEN HUMAN MILK. J. LORENZO Y DEAL, Arch. de pediat. d. Uruguay **8**:733 (Dec.) 1937.

The author emphasizes the need and importance of the procedure for freezing milk.

Eight cases are presented in which he used this preparation. He claims good results, especially because it was used in summer, when there are more gastrointestinal disorders. He has used the preparation even after two hundred and eighty days of storage.

SCHLUTZ, Chicago.

BACTERIAL CONTENT AND BACTERIOLYTIC ACTION OF HUMAN MILK. J. A. BAUZA and M. C. SAIZAR, Arch. de pediat. d. Uruguay **9**:273 (May) 1938.

The authors confirm the report of the presence of a lysoenzyme in human milk. It is active and varies with the kind of milk. The bacterial titer is low in twenty-four hours but increases from forty-eight hours on.

SCHLUTZ, Chicago.

RAW OR BOILED BREAST MILK. W. CATEL, Med. Klin. **34**:215 (Feb. 18) 1938.

The article is a countercriticism of an article by Kayser criticizing Catel's stand regarding stations for the distribution of boiled cow's milk and breast milk. Catel reviews his work, which tends to show that boiled milk is inferior to artificial food for infants and that even raw expressed breast milk is inferior to the milk obtained by the nursing infant. He contends that prevalent ideas regarding the virtue of boiled breast milk rest mainly on general impressions. He thinks the high price at which boiled breast milk is sold is unjustified.

SIEMSEN, Chicago.

GASEOUS METABOLISM IN CHILDHOOD: V. BASAL METABOLISM IN CHILDREN WITH ABNORMAL BODY DIMENSIONS. M. DE BRUIN, Nederl. tijdschr. v. geneesk. **82**:1557 (April 2) 1938.

With the aid of the results obtained in a study of 107 children with abnormal body dimensions, an attempt was made to determine a standard for determining the basal metabolic rate in children with abnormal body dimensions.

The following directions for calculating the standard basal metabolic rate are proposed: (*a*) For fat boys weighing up to 35 per cent above the standard weight, calculate the rate by the actual weight; for those showing higher degrees of obesity, by the standard weight for the actual length, increased by one third of the excess over the standard weight. (*b*) For fat girls weighing up to 20 per cent above the standard weight, calculate the rate by the actual weight; for those showing higher degrees of overweight, by the standard weight increased by one third of the excess over the standard weight. (*c*) For lean boys and lean girls, calculate the rate by the actual weight. (*d*) For well proportioned too tall or too short children, calculate the rate by the actual weight.

VAN CREVELD, Amsterdam, Netherlands.

## Vitamins; Avitaminoses

THE VITAMIN B COMPLEX AND FUNCTIONAL CHRONIC GASTRO-INTESTINAL MALFUNCTION: A STUDY OF TWO HUNDRED AND TWENTY-SEVEN CASES. H. BORSOOK, P. DOUGHERTY, A. A. GOULD and E. D. KREMERS, Am. J. Digest. Dis. **5**:246 (June) 1938.

This is a study of a series of 227 cases of chronic gastrointestinal malfunction. These cases were studied for not less than three months and some for as long as four years.

In nearly all the patients continued ingestion of large amounts of the vitamin B complex was of marked benefit. The order in which symptoms were relieved was usually as follows: constipation (in most cases within from two to four weeks), abdominal pain, lack of appetite, headaches and the feeling of fatigue. "Gas" was usually the most persistent complaint.

The results are interpreted as indicating a widespread partial vitamin B deficiency in man; i. e., many, if not most, persons require for normal gastrointestinal function several times the minimal amounts of the vitamins required to prevent severe deficiency diseases, such as beriberi and pellagra.

MORRISON, Savannah, Ga.

THE VITAMIN C CONTENT OF CERTIFIED MILK AT THE TIME OF CONSUMPTION. F. V. WEST and J. C. WENGER, Am. J. Digest. Dis. **5**:251 (June) 1938.

This report represents a study of the actual vitamin C or ascorbic acid content of certified milk at the time it is consumed in the home. In determinations made on thirty-four hour certified milk the average minimal vitamin C content of the milk of Holstein cows approximated 262 international units per quart, and that of the milk of Guernsey cows 284 international units.

The 720 titrations of vitamin C content in certified milk from 108 cows indicate that the milk concerned may be considered a valuable food because of its vitamin C content.

MORRISON, Savannah, Ga.

SPECIFIC DERMATOSES DUE TO VITAMIN A DEFICIENCY. J. B. YOUMANS and M. B. CORLETTE, Am. J. M. Sc. **195**:644 (May) 1938.

Youmans and Corlette describe 6 cases in which specific lesions of the skin were caused by deficiency of vitamin A, including the results of histologic studies and the response to treatment. In some of the cases the lesions presented were of the dry, horny, papular type described by Frazier and Hu, Loewenthal and others. In other cases an acne-like lesion was presented.

They discuss the various types of lesions described in the literature of this and foreign countries.

HENSKE, Omaha.

CEVITAMIC ACID CONTENT OF FETAL BLOOD. C. P. MANAHAN and N. J. EASTMAN, Bull. Johns Hopkins Hosp. **62**:478 (May) 1938.

The method of Tillmans, Hirsch and Hirsch was used, and potassium cyanide was added to the blood. The concentration of ascorbic acid in the blood of the fetus is regularly almost three times that in the maternal blood. This suggests that the placenta exerts a selective action on this vitamin, confirming the studies of Braestrup.

LYTTLE, New York.

CELLULAR CHANGES IN THE ANTERIOR HYPOPHYSES OF VITAMIN-A DEFICIENT RATS. T. S. SUTTON and B. J. BRIEF, Endocrinology **23**:211 (Aug.) 1938.

In the hypophyses of vitamin A deficient rats of both sexes a significant increase in "basophilic" cells was found. The increase was greatest in males. The observation indicates that vitamin A deficiency has a partial castration effect on the hypophysis.

JACOBSEN, Buffalo.

INFLUENCE OF ASCORBIC ACID ON ANAPHYLAXIS IN GUINEA PIGS. S. RAFFEL and R. R. MADISON, J. Infect. Dis. **63**:71 (July-Aug.) 1938.

Daily parenteral administration of ascorbic acid to 16 guinea pigs prior to and during a period of active sensitization caused complete inhibition of the hypersensitive manifestations—contraction of the uterine horn and anaphylaxis—in only 2 of the animals.

The development of precipitins was marked in these animals that were treated with ascorbic acid as contrasted with untreated controls.

The presence or absence of circulating antibody did not influence the hypersensitive reactions by an antianaphylactic or other effect.

Single preshock injections of ascorbic acid into passively sensitized guinea pigs apparently had no effect on their sensitivity.

Ascorbic acid added to the suspension fluid in no way altered the sensitivity of excised uterine horns of passively sensitized animals.

TOOMEY, Cleveland.

DANGER OF ARTIFICIAL VITAMIN FEEDING. A. VERGARA E., Rev. mex. de puericultura **8**:184 (March) 1938.

No one doubts that vitamins are necessary for the proper functioning of the human body. Vitamins may be obtained in two ways, by eating foods rich in vitamins or by taking vitamins in artificial form. It is necessary to feed proper amounts of the various vitamins to produce normal nutrition, but it is desirable not to continue feeding the vitamins in excess. HERRON, Monroe, La.

## Hygiene; Growth and Nutrition; Public Health

INFANT MORTALITY IN PARAGUAY. R. ODRIOSOLA, Bol. Inst. internac. am. de protec. a. la infancia **12**:28 (July) 1938.

Odriosola talks about the causes of mortality in infants and refers to the lack of doctors in towns and in the country which results in 75 per cent of the infant population in Paraguay being cared for by charlatans. To avoid this evil, the author proposed to the Council of Hygiene in 1931 that sanitary associations be created throughout the country; and in 1935, when he was rector of the medical school, he planned the creation of the Mother and Child Institute. Moreover, he advocates that diverse institutions for mother and child welfare should be created co-ordinating all the means of defending the health and welfare of the child under the administration of an organized association, that is, the Child Council or the Department for Child Protection. FROM EDITOR'S SUMMARY.

TUTELAR MAGISTRACY OUGHT TO COMPLETE THE WORK OF THE JUVENILE COURT. R. BERRO, Bol. Inst. internac. am. de protec. a la infancia **12**:59 (July) 1938.

The substance of this article is suggested in the title. The tutelar judge should be more of a father or guardian than a judge. LESLIE, Evanston, Ill.

MOTHER AND CHILD WELFARE CENTERS. W. PIAGGIO GARZÓN, Bol. Inst. internac. am. de protec. a la infancia **12**:84 (July) 1938.

The author establishes that protection of the child without simultaneous protection of the mother is not efficient. He presents a summary of the work of different social aid centers and of legislative measures for prenatal and postnatal protection. He also lists the special qualities of these centers and critically reviews their work. EDITOR'S SUMMARY.

TREATMENT OF NEGLECTED CHILDREN; MEANS OF PROTECTION; NO ASYLUMS; FAMILY HOMES. L. B. PRIETO F., Bol. Inst. internac. am. de protec. a la infancia **12**:108 (July) 1938.

In Venezuela, writes Prieto, the scene of neglect that childhood presents is dreadful; gloomy misery is seen everywhere. Many children are spoiled and their possibilities destroyed by employment in the street. He charges that while in all the countries of the world measures are taken to prevent such havoc and neglect of children, Venezuelans remain indifferent to the problem. He urges that organizations of a social character be established to aid and protect children. This aid, he states, must be given not as charity but as an imperious social duty, "for dependent children need not charity but social aid."

FROM EDITOR'S SUMMARY.

SPEECH AT THE FIRST VENEZUELAN CONGRESS ON "THE CHILD." PASTOR OROPEZA, Bol. Inst. internac. am. de protec. a la infancia **12**:119 (July) 1938.

Oropeza emphasizes that for the first time in his country a meeting of scientific men took place to study the Venezuelan child from the social point of view.

The child's problem is economic and educational. Child welfare work should be integral from the beginning, a conception which involves the vast and complex problem of eugenics. At present pediatricians should devote their efforts to the struggle against syphilis and alcohol, two poisons that leave indelible traces in the offspring. Venezuelans drink too much. The danger in the consumption of alcohol should be preached continually, and the efficacy of sport and the necessity of work must be pointed out to youth. Venezuelan municipal governments must create sport centers and encourage sport.

The author then refers to the mother and baby, as well as to the correlative problems of insurance of maternity and premiums for breast feeding; also, to the necessity of organizing kindergartens for preschool children and to that of establishing good schools for the elder ones.

Illegitimacy, with a high percentage of child abandonment, calls for fundamental changes in habits and in legislation; in the same way it is urgent that a number of organizations be established or that support be given those already started, and all of them should be placed under the technical inspection of one single association, the binomial mother-child being always borne in mind. All child welfare workers should concentrate on the aim of strengthening the home, the biologic cell of humanity.

Oropeza calls attention to the program formulated by the Fourth Child's Pan-American Congress, which was restated in the seventh congress.

EDITOR'S SUMMARY.

QUALIFICATIONS FOR CARE OF A CHILD. J. C. BABICKI, Zycie Mlodych **7**:41 (Feb.) 1938.

Many of those who take care of children are not qualified. An important point in taking care of a child is to know the child. However, in order to know a child, one has to have intelligence, knowledge and experience.

KRUPINSKI, Chicago.

NECESSITY AND POSSIBILITY OF TRAINING YOUTH OF FAMILIES RECEIVING PUBLIC HELP. H. DINTER, Zycie Mlodych **7**:45 (Feb.) 1938.

There is a great need for training of this type. One sees thousands of youths, healthy, intelligent, full of energy, whose talents are wasted. Their salvation requires highly schooled preceptors in well organized institutions, where the youths could be trained according to their leanings and qualifications so that they may become useful to the community and to the country. KRUPINSKI, Chicago.

REPORT OF FIFTEEN YEARS' WORK OF A COMMITTEE ON THE CARE OF CHILDREN ALONG EDUCATIONAL LINES. B. KRAKOWSKI, Zycie Mlodych **7**:74 (March-April) 1938.

Much has been accomplished along the lines of care of children, although the beginning was hard. The author mentions the names of all those who were instrumental in developing the institution described. Much work has been done in dissemination of knowledge relating to care of children, papers have been written, and research has been done. The efforts were not in vain; now the workers reap the harvest.

KRUPINSKI, Chicago.

LOOKING BACKWARD. J. C. BABICKI, Zycie Mlodych **7**:79 (March-April) 1938.

Since 1928 much has been accomplished and many improvements have been made in the care of children in Poland. Consumption of alcohol in general has decreased very much. Many public institutions have been built for children. The

personnel for taking care of young people is well trained and capable. The relationship between families and personnel of institutions has been improved. Hygienic conditions in villages are much improved. Many summer camps for children have been opened. Much has been accomplished in ten years, but much remains to be done in the future.

KRUPINSKI, Chicago.

## Prematurity and Congenital Deformities

HURLER'S SYNDROME (GARGOYLISM): A SUMMARY OF THE LITERATURE AND A REPORT OF A CASE WITH AUTOPSY FINDINGS. R. J. KRESSLER and E. E. AEGERTER, J. Pediat. **12**:579 (May) 1938.

This is a report of the case of a patient who showed a congenital systemic disorder. The first symptom noted was clouding of the corneas, which occurred at the age of 5 months. At the age of 6 months skeletal abnormalities were noted. Subsequently definite retardation in both physical and mental development occurred, with enlargement of the liver and spleen. At the age of 7½ years paroxysmal attacks of dyspnea with cyanosis, dependent edema and marked cardiac enlargement were noted. Death followed at the age of 8½ years, as a result of cardiac failure. Autopsy revealed an infiltration of a lipid-like substance in most of the tissues but chiefly in the liver, lymph nodes and anterior lobe of the pituitary. The autopsy failed to explain either the skeletal abnormality or the corneal opacities. The causal factor in this disease is unknown, but a dysfunction of metabolism, probably of that of a complex lipid, appears to be the most likely cause. Because of lesions of the nerves similar to those characteristic of juvenile amaurotic familial idiocy and Niemann-Pick disease and a disturbance in the metabolism of a lipid resembling that observed in patients with Niemann-Pick, Hand-Schüller-Christian and Gaucher syndromes, the authors believe that this syndrome should be classified as a fifth disease in the category of the lipidoses.

RAUH, Cincinnati.

EHLERS-DANLOS SYNDROME. A. C. RAMBAR, J. Pediat. **12**:592 (May) 1938.

This is the report of a case of a syndrome described by Ehlers in 1900: This syndrome includes the following symptoms: (1) hyperelasticity and hyperlaxity of the skin; (2) fragility of the skin and blood vessels, with cutting or splitting of the skin or the production of hematomas and pseudotumors following trauma, and (3) hyperflexibility of the joints. A brief review of the literature is included in the article, together with enumeration of the various theories as to the etiologic factors. The only treatment which has been found of any value has been that of protecting the skin against trauma.

RAUH, Cincinnati.

INFLUENCE OF FACTORS BEFORE AND AT TIME OF DELIVERY ON PREMATURE MORTALITY. B. B. BREESE JR., J. Pediat. **12**:648 (May) 1938.

Breese presents a statistical study of the influence of maternal factors and of factors in the obstetric management of deliveries on the mortality rate of premature infants as found in a study of 987 premature infants. The most important factor influencing the mortality rate of premature infants is the size at birth. The weight at birth is used as the criterion of size. Breese presents a method in which the influence of the weight at birth is eliminated in the estimation of the influence of other factors on the mortality rate of premature infants. He found that such maternal factors as multiple pregnancies and toxemia have relatively little effect on the mortality rate of premature infants who are born alive. The one exception to this is hydramnion, which exerts a very harmful effect on this mortality rate. The age of the mother, provided she is not over 40 years of age, has very slight effect on the rate. Infants of women over 40 years have a slightly higher mortality rate than would be expected on a basis of weight. Among the obstetric factors, vertex delivery is slightly safer than breech delivery. Induction of labor

has no deleterious effect on the rate in question, but medical induction seems safer than induction by bag. Cesarean section seems to be a safe method of delivery. Forceps delivery seems safer than any other mode of delivery. Ether seems the safest anesthetic for the premature infant. The use of morphine with other drugs is dangerous, and the failure to use any anesthetic is dangerous. The most important group to be considered in reducing the mortality rate of premature infants is the group of infants whose deliveries were induced—15 per cent of this series. If the infants of this group could be brought nearer to term, the mortality rate might be reduced. However, because of the danger to both infant and mother in many cases if the infant is carried closer to term, little improvement in the mortality rate can occur in this group. The best hope of reduction in the mortality rate of premature infants still lies in the care of these infants after birth.

RAUH, Cincinnati.

PARALLEL DUPLICATION OF THE FACE IN AN ANENCEPHALIC FETUS. G. MAIZELS, J. Obst. & Gynaec. Brit. Emp. **45**:679 (Aug.) 1938.

The fetal monsters known as diprosopi may be subdivided into three groups: those in which there is one mouth with duplication of the upper part of the face; those in which increasing duplication and divergence occur inferiorly, and those in which the duplication is symmetric. Maizels describes an anencephalic monster with a symmetric duplication of the face in which each face had a mouth, nose, lateral ear and eye. The medial eye was a fusion; the medial ear was represented only by a dimple. The mandibles were separate, but the malar bones were fused. There was also partial duplication of the spinal column.

ADAIR and POTTER, Chicago.

INTRA-UTERINE AMPUTATIONS AND ANNULAR CONSTRICTIONS IN A LIVING INFANT, NOW A CHILD OF FOUR, DUE TO AMNIOTIC ADHESIONS RESULTING FROM OLIGOHYDRAMNIOS. Y. N. AJINKYA, J. Obst. & Gynaec. Brit. Emp. **45**:692 (Aug.) 1938.

Ajinkya describes a child 4 years of age suffering from constricted areas on arms and legs and multiple constrictions and amputations of the digits. To all of these areas portions of amniotic membrane were attached at the time of birth. He believes that the deformities are due to an oligohydramnion which permitted the formation of adhesions between the fetus and the amnion.

ADAIR and POTTER, Chicago.

## Newborn

MILIARY TUBERCULOSIS IN A NEWBORN INFANT. G. M. WHITE and D. F. W. PORTER, Canad. M. A. J. **39**:165 (Aug.) 1938.

This is a detailed report of a case of miliary tuberculosis beginning on the fourth day after birth. Careful examination of all persons who had had possible contact with the baby seemed to rule out the likelihood of outside infection. The mother showed in the apexes of her lungs two calcified areas with no surrounding reaction. It is concluded that the infection was blood borne and that it occurred in the last two weeks of intrauterine life. The placenta was macroscopically normal but was not examined microscopically, as the baby seemed normal at birth.

MOORE, Omaha.

INTRACRANIAL BIRTH INJURY. A. J. MAUZEY, Illinois M. J. **74**:156 (Aug.) 1938.

According to Mauzey, intracranial injury of infants at the time of birth occurs during protracted, spontaneous and operative deliveries. A contributing

part is played by hemorrhagic disease of the newborn. Prematurity accounts for intracranial injury in two thirds of the infants so injured. In many cases of so-called intracranial hemorrhage the condition may be cerebral edema. When cerebral hemorrhage occurs, it leaves a damaged brain. As to treatment, the greatest value attaches to prophylaxis.

BARBOUR, Peoria, Ill.

EPIDEMIC DIARRHEA OF THE NEWBORN. W. H. BEST, J. A. M. A. **110**:1155 (April 9) 1938.

This article describes the recognition of epidemic diarrhea in nurseries for the newborn in hospitals of the city of New York. These epidemics involve many of the exposed newborn babies, and of those involved almost half succumb. They present diarrhea, listlessness, distention and shock. There are loss of weight and dehydration. All phases of the disease are discussed. Its occurrence produces a problem of public health, and the article includes the regulations prepared for and adopted by the New York State Board of Health for prevention and care of this condition.

HEERSMA, Kalamazoo, Mich.

BLOOD PLATELETS IN THE NEWBORN. F. RASI and M. BOLLETTI, Riv. di clin. pediat. **36**:430 (May) 1938.

Observations were made on the blood of 10 newborn infants within one hour, twenty-four hours, forty-eight hours and five days after birth. The changes in each case were consistent with the averages given in the following table.

| | Platelets | Red Blood Cells | Reticulocytes |
|---|---|---|---|
| At birth | 192,000 | 5,170,000 | 119,000 |
| 24 hours | 511,000 | 6,520,000 | 280,000 |
| 48 hours | 354,000 | 5,900,000 | 178,000 |
| 5 days | 249,000 | 5,230,000 | 81,000 |
| Older children | 222,000 | 4,360,000 | 39,000 |

HIGGINS, Boston.

RITTER'S DISEASE AND PEMPHIGUS NEONATORUM. E. PELUFFO and A. RAMÓN GUERRA, Arch. de pediat. d. Uruguay **9**:233 (April) 1938.

An epidemic of pemphigus neonatorum developed in the obstetric clinic of the Russel-Pereira Hospital, Montevideo, Uruguay. The prognosis was good, the only complications being local infections forming pyoderma. In only a single infant did the disease take a malignant course, with development of marked exfoliation, purpura and generalized epidermolysis (Ritter's disease). This infant died five days after the onset.

SCHLUTZ, Chicago.

HEMORRHAGE OF THE NEWLY BORN. J. C. TRAVERSARO, Rev. méd. latino-am. **23**:942 (May) 1938.

Traversaro describes his experience with hemorrhage in the newborn infant and reviews the literature extensively. A large number of infants die in the first week of life because of hemorrhage. Such hemorrhage results either from obstetric trauma or from dyscrasia of the blood. Prematurity predisposes the infant to intracranial hemorrhage. Therefore, as a prophylactic measure, Traversaro advises that gynecologists look to the causes of premature birth. A spinal puncture should be made when intracranial hemorrhage is suspected. Treatment consists in intramuscular injection of blood; if the hemorrhage is severe, blood should be given intraperitoneally and intravenously.

DWYER, Kansas City, Mo.

TREATMENT FOR SERIOUS NEONATAL JAUNDICE. H. KAWAKAMI and E. YOGO, Jap. J. Obst. & Gynec. **21**:218 (May) 1938.

Three infants suffering from severe jaundice who were given magnesium sulfate and hydrochloric acid by gavage promptly recovered. The first infant to be treated represented a fifth pregnancy; the preceding 4 infants had succumbed following the development of fever and jaundice a few days after birth. The other 2 infants treated were the first born and second born of their respective mothers. The authors believe that severe jaundice of the newborn is due to partial obstruction or nonfunction of the bile ducts and not to hemolysis of erythrocytes. The drugs recommended are believed to stimulate the flow of bile into the intestine.

ADAIR and POTTER, Chicago.

A NEWBORN INFANT WITH INTRICATE DEFORMITIES. K. HORIE and S. KONDO, Jap. J. Obst. & Gynec. **21**:230 (May) 1938.

A malformed fetus is described. The abnormalities consisted in an umbilical hernia with absence of the umbilical cord, anal atresia, cystic kidneys, spinal rachischisis, scoliosis, right talipes equinovalgus, a rudimentary left lower extremity and minor defects. The cause is unknown.

ADAIR and POTTER, Chicago.

INSERTIO FURCATA FUNICULI UMBILICALIS. O. HERBERZ, Acta obst. et gynec. Scandinav. **18**:336, 1938

Insertio furcata funiculi umbilicalis possibly occurs oftener than is generally acknowledged. All placentas must be examined in this respect, and one should observe not only the cases in which the bifurcation lies at a great distance but also those in which it is situated from 3 to 4 cm. from the surface or the edge of the placenta. Herberz illustrates this with 6 case histories which he collected in about two years (total number of deliveries about 6,000). In 2 cases the child died during labor; in 1 case a passing asphyxia was noted; in the other cases the condition terminated without complications. Herberz comes to the conclusion that this anomalous insertion of the cord can be of a certain obstetric interest and should be remembered when intrauterine asphyxia is detected.

ADAIR and POTTER, Chicago.

## Acute Contagious Diseases

MENINGOCOCCIC MENINGITIS AND ACUTE MENINGOCOCCEMIA. C. V. CRASTER and H. SIMON, J. A. M. A. **110**:1069 (April 2) 1938.

Craster and Simon review the subject of meningococcic meningitis and describe the clinical entity meningococcemia. Typical of the condition is the cutaneous eruption, especially the petechial rash, which often occurs and precedes any evidence of meningitis.

Several important points by which meningococcic infection in infants differs from that in older victims are brought out. In infancy early signs do not point to the central nervous system.

Symptoms of unusual interest occurring in this disease, here described, are those due to adrenal hemorrhages, mental changes and arthritis.

HEERSMA, Kalamazoo, Mich.

SENSITIVITY OF THE DIPHTHERITIC HEART TO DIGITALIS. C. W. EDMUNDS, R. G. SMITH and C. A. MOYER, J. Pharmacol. & Exper. Therap. **61**:286 (Sept.) 1937.

The authors found that diphtheritic dogs succumbed to much smaller doses of digitalis than did normal dogs. Cats that had received diphtheria toxin some days

previously also succumbed to smaller doses of digitalis, given by vein, than did normal animals. Digitalis and diphtheria toxin both act on the cardiac conducting system, and these authors agree with von Kiss that a full dosage of digitalis is to be avoided in cases of injury to the conducting system, as the drug possesses a peculiar affinity for this system, and if this system is damaged by the toxin, even to a slight degree, a therapeutic dose of digitalis may produce a complete block from a latent one.

In spite of occasional reports to the contrary, the bulk of experimental evidence seems to indicate that digitalis, if used at all in diphtheria, should be used with extreme caution.

PILCHER, Cleveland.

POLIOMYELITIS: FACTS AND FALLACIES. L. L. LUMSDEN, South. M. J. **31**:465 (May) 1938.

Lumsden feels that as regards the disease which is called poliomyelitis knowledge of its specificity, causes, pathogenesis, diagnosis, therapeusis and prevention is as yet inadequate and indefinite. Much more work on these problems is urgently and critically needed. It should include epidemiologic, laboratory, entomologic, zoologic, botanic, topographic and meteorologic studies, duly prolonged, intensive and wide in scope, extending from the Arctics to the equator.

SCHLUTZ, Chicago.

OBSERVATIONS ON THE PATHOLOGY AND PATHOGENESIS OF ACUTE POLIOMYELITIS IN THE RECENT EPIDEMIC IN ARKANSAS. A. F. DEGROAT, South. M. J. **31**:475 (May) 1938.

The 1937 epidemic of poliomyelitis in Arkansas was complicated little if at all by other viral diseases of the nervous system. This was quite contrary to the situation that had been anticipated. A study of the pathologic material obtained in this epidemic revealed no satisfactory evidence that the portal of entry of the virus had been the olfactory apparatus.

SCHLUTZ, Chicago.

INTRATHECAL SULPHANILAMIDE IN MENINGOCOCCAL MENINGITIS. A. ELDAHL, Lancet **1**:712 (March 26) 1938.

Twelve children under 4 years of age were treated for meningococcic meningitis with intrathecal and intramuscular injections of a 0.8 per cent solution of sulfanilamide. The amount injected into the spinal canal was from 5 to 30 cc., and the intramuscular dose was from 35 to 150 cc., according to the weight of the patient. Three patients died (25 per cent), whereas the average fatality rate for children under 4 in the past six years (i. e., before the introduction of sulfanilamide therapy) was 70 per cent.

The conclusion so far reached about the use of sulfanilamide in the treatment of meningococcic meningitis is that this drug has little effect if given exclusively by mouth and intramuscularly but that if it is given intrathecally as well it is valuable.

LANGMANN, New York.

THE SCHICK REACTION AND CIRCULATING DIPHTHERIA ANTITOXIN IN MAN. H. J. PARISH and J. WRIGHT, Lancet **1**:882 (April 16) 1938.

Parish and Wright confirmed the observations of Jensen and others that there is no certain level of antitoxin (Schick level) such that when the titer determined is above it the subject concerned may be regarded as a negative reactor and when the titer is below it the subject may be held to be a positive reactor to the Schick test. Nevertheless, there is a much higher level of circulating antitoxin in groups giving a negative than in those giving a positive reaction.

The authors comment on the potential immunity of persons who have little circulating antitoxin but who react negatively to the Schick test.

The Schick test has been proved to be of value in many immunization campaigns, but a negative reaction may not in every case indicate immunity sufficient to withstand attack by virulent gravis or intermediate strains of the diphtheria organism.

To maintain a sufficiently high level of resistance, the periodic injection of prophylactic antitoxin into persons with a negative, as well as into those with a positive, reaction may be considered advisable. LANGMANN, New York.

TREATMENT OF MENINGOCOCCAL MENINGITIS WITH SULPHANILAMIDE. T. CRAWFORD and G. B. FLEMING, Lancet **1**:987 (April 30) 1938.

This is a report on 10 children, 4 of whom were less than a year old. Only one died—a baby less than a year old and ill for six weeks.

Prontosil soluble (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid) was given intramuscularly and sulfanilamide by mouth, and to the last 4 patients a 1 per cent solution of sulfanilamide was given intrathecally.

The concentration of sulfanilamide in the cerebrospinal fluid seemed to bear no relation to the course of the disease or to the speed with which the fluid was sterilized. Intrathecal injection rendered the cerebrospinal fluid sterile in cases in which oral and intramuscular administration had failed to do so.

LANGMANN, New York.

SERUM AND SULPHANILAMIDE IN ACUTE MENINGOCOCCAL MENINGITIS. H. S. BANKS, Lancet **2**:7 (July 2) 1938.

This is a report of 113 sporadic and seasonal cases of acute meningococcic meningitis.

For 38 patients treated with intravenous injections of large doses of serum, combined with intrathecal injections of serum twice daily during the first five days, the fatality rate was 16 per cent.

For 59 patients (including 10 infants) treated with both serum and sulfanilamide, the fatality rate was 11.8 per cent.

Of 16 selected patients of favorable age grouping who were treated with sulfanilamide alone, 15 showed rapid recovery.

The age period from 5 to 20 years is the most favorable for recovery.

The former high rate of mortality in infants with meningococcic meningitis seems to be yielding to sulfanilamide therapy. Experimental and clinical evidence is so far in favor of combined serum and drug therapy, especially for children severely affected.

LANGMANN, New York.

DISTURBANCE OF THE VEGETATIVE NERVOUS SYSTEM AND MYOCARDITIS IN DIPHTHERITIC INTOXICATION. G. FRONTALI, Riv. di clin. pediat. **36**:385 (May) 1938.

Frontali in 1923 reported an accentuation of the oculocardiac reflex in diphtheritic paralysis. Recently Castelli-Borgiotti (*Riv. di clin. pediat.* **35**:886 [Oct.] 1937) in confirming this finding expressed the opinion that this accentuation is a manifestation of myocarditis. Frontali reasons that, while myocarditis may be present, the effect of atropine and the sphygmographic and electrocardiographic records indicate that the accentuation of the reflex is extracardiac and due to neuritis of the vegetative nervous system. HIGGINS, Boston.

NONPARALYTIC HEINE-MEDIN DISEASE. M. J. CARRIL and B. D. MARTINEZ, Arch. argent. de pediat. **8**:1245 (Dec.) 1937.

The authors present 35 cases of acute anterior poliomyelitis. They stress the epidemiologic significance of nonparalytic forms and the importance of the examination of the cerebrospinal fluid.

They suggest that lumbar punctures should be made during all epidemics of acute infections presenting griplike features and slight meningeal symptoms, as vague pains, stiffness of the neck and spine and headache.

SCHLUTZ, Chicago.

POSTINFECTION ENCEPHALITIS. A. GAREISO and P. O. SAGRERAS, Arch. argent. de pediat. **8**:1281 (Dec.) 1937.

The authors describe the symptoms and course of encephalitis following whooping cough, diphtheria, pneumonia and measles. Children frequently present psychic or neurologic syndromes and at such times should be examined for some acute infection. There is no special type for each infection, and no relation is apparent between the severity of the infection and that of the encephalitis. The infection may also be caused by vaccination against smallpox and by varicella.

SCHLUTZ, Chicago.

A FATAL CASE OF ALASTRIM (MILK POX) IN AN INFANT. J. M. DA ROCHA, Arch. de pediat., Rio de Janeiro **10**:449 (June) 1938.

Alastrim, or variola minor, which resembles true smallpox (variola major) in the character and distribution of the lesions, is fairly common in Brazil. It differs from variola major in the absence of fever, the lack of scarring and the generally benign course. The mortality in a series of cases is estimated as between 0.5 and 2 per cent. This case was reported because of the fatal termination. The child was 2 years of age. Its illness followed the usual mild course but was complicated by anuria. Permission for an autopsy was not obtained.

SANFORD, Chicago.

NASAL REVACCINATION AGAINST SMALLPOX IN THE PRACTICE OF PEDIATRICS. D. GYURKE, Deutsche med. Wchnschr. **64**:1211 (Aug. 19) 1938.

In 1917 Gins found that the mucous membrane of the upper part of the respiratory tract is the main channel for the excretion of the virus of smallpox during the clinical disease. He and his co-workers also found the virus of variola in secretions from the throats of 6 healthy infants who had been vaccinated three days previously.

On the basis of Gin's experiences, Gyurke set out to find whether nasal revaccination against smallpox would not be more effective in human beings than the customary cutaneous revaccination. He does not suggest the nasal method for first vaccination. Half a drop of tested virus vaccine mixed with 4 drops of saline solution was applied on cotton in both nostrils for five minutes. This treatment was followed by a cleasing of the nostrils, nares and surroundings with alcohol.

Fifty children were first vaccinated cutaneously against smallpox. From one to five years later they were revaccinated nasally and fourteen days later were tested for immunity by cutaneous revaccination. All failed to react to the cutaneous revaccination, which was interpreted as a sign of immunity.

Another group of children was vaccinated and one to five years later revaccinated cutaneously. Fifty of the ones who gave no reaction at revaccination were tested ten days later by the nasal method. Except 7, all gave local reactions on the mucous membrane of the nose; 19 showed moderate fever and 18 some rhinitis.

The author concludes from these results that nasal revaccination is more effective than cutaneous, and that a reaction of the nasal mucous membrane to the application of a 1:8 dilution of the virus of smallpox points to the presence of mild susceptibility to this disease better than does a reaction to cutaneous revaccination. He considers the local reactions in the nose and the mild fever as insignificant and the greater danger of encephalitis as unproved.

[The author has described an interesting but daring innovation. Abstractor.]

KERESZTURI, New York.

TREATMENT OF SEQUELAE FOLLOWING POLIOMYELITIS. J. HASS, Wien. klin. Wchnschr. **49**:1670 (Dec. 10) 1937.

Hass points out that there are many methods of restoring in part or in full the function of muscles paralyzed as a result of poliomyelitis. In over half the cases true poliomyelitis results in more or less serious muscular dysfunction, which demands the physician's best care. Unfortunately, many contractures which could have been prevented are allowed through neglect to develop beyond possibility of correction.

The author urges beginning orthopedic treatment at the earliest possible date, while the patient is still in bed during the convalescent stage. The child should be kept flat on the back, and the mattress should be supported by a board to keep it from sinking in. The knee joints should be procumbent and weighted down with a 3 Kg. sandbag. To prevent deformity of the foot the author fastens on the foot a cushioned splint which keeps the foot at a right angle with the ankle. The arms should be held, as far as possible, in right-angled abduction and outward rotation, since in this position overstretching of the deltoid muscle and of the muscles from the shoulder blade to the humerus will be avoided. Hass recommends the right-angled position for the elbow and a slight dorsal flexion for the wrist joint.

It is especially necessary to take care of the back, since the paralysis often affects the muscles of the trunk. The patient when sitting up should be supported by a back rest. Best of all is lying on the stomach, at least occasionally. Instead of this, one often sees patients bolstered upright in bed, with hips and knees weakly supported, and even sitting up without any brace. The usual results are hip and knee contractures and paralytic scolioses which are beyond the aid of orthopedics.

If a contracture has developed, the Mommsen excitation treatment is recommended. Its value lies in the fact that it requires a minimum of effort; the contracture grows out of the impulses which lie below the stimulus threshold and hence are neither painful nor harmful. As a rule, the correction of the contracture is accomplished in fourteen days, and only in cases in which the contracture is severe are operative measures necessary.

A second and important part of the treatment during this period is that for strengthening the musculature. This is accomplished through baths, massage, stimulation by electricity and gymnastics. Each affected muscle should be treated, but the author cautions against inexpert manipulation, which can do more harm than good. Electric treatment should never overstep the threshold of stimulation in the particular muscle. Leduc's current applied according to Liebesny's method or with the help of the Ebel tonisator or of the electropan (*Kowarschik*) seems to be effective. In the gymnastic treatment overexertion should be studiously avoided; active exercise for short, gradually lengthened periods should be the rule.

The Warm Springs, Ga., method of systematic exercise under water has the advantage of accomplishing results quicker than ordinary exercise, and the thermal bath itself has a favorable effect.

The patient should be put on his feet as quickly as possible; walking is the best exercise for the musculature; in fact, it is the only means of counteracting the threatened atrophy of the knee and other joints. Unfortunately, it is still not sufficiently realized that almost every victim of infantile paralysis can be put on his feet, at least with the help of apparatus. The author recommends the half circle type of device, which leaves the musculature free, with elastic to support its weakness. When the paralysis is severe, automatic braces for the joints are used to keep the legs steady. Often it is possible by means of static support of the joint (the hip joint in forward position, the knee joint to the rear) to achieve stabilization without braces, to which the patient quickly accustoms himself.

ABT, Chicago.

ENDOCARDITIS FOLLOWING DIPHTHERIA. V. JEDLICKA, Časop. lék. česk. **75**:402 (April 3); 440 (April 10); 494 (April 17); 510 (April 24) 1936.

Jedlicka cites 10 cases of endocarditis diphtheriae and presents 4 cases which he studied completely. He discards 3 cases as not definite and disqualifies 4 more because the diphtheria organisms cultivated from the endocardium were not pathogenic for guinea pigs. Of these cases, virulent diphtheria bacilli were recovered only in 1 instance reported by Herzog, 2 cases reported by Chiari and 4 cases reported by Jedlicka. In the cases reported by Jedlicka, a girl of 10 acquired verrucous growths on the mitral valve, a boy of 8 acquired polypoid growths on the mitral valve, a girl of 9, who died with symptoms of hemiplegia, had vestibular thrombosis of the left ventricle with generalized scattered emboli, and a girl of 4, with a scarlatina-diphtheria sequence, had otitis media from which the diphtheria organism was cultivated and at autopsy had ulcerative vegetations on the tricuspid and mitral valves. In all 4 of the cases diphtheria organisms virulent for guinea pigs were isolated from the blood and the cardiac valves. STULIK, Chicago.

THE VITAMIN C CONTENT OF THE BRAIN, VITREOUS HUMOR AND CEREBROSPINAL FLUID IN EXPERIMENTAL RABIES. T. UNO, Orient. J. Dis. Infants **21**:79 (May) 1937.

Assuming that a relationship may exist between the changes in the meninges of rabbits inoculated with rabies virus and the vitamin C content of the central nervous system, Uno investigated (by the colorimetric method) the vitamin C content of the brain, vitreous humor and cerebrospinal fluid. However, the results demonstrated no significant variations from the normal. KATO, Chicago.

POSTSCARLATINAL NEPHRITIS AND ITS PROGNOSIS. T. SÄLLSTRÖM, Acta pædiat. (supp. 1, art. 1) **20**:1, 1937.

This report is based on statistics obtained from the records of the Stockholm Hospital for Contagious Diseases between the years 1920 and 1934. During this period 11,250 patients with scarlet fever were treated in that institution. The ages of the patients varied from a few months to 25 years; the modal age was 7 years. Despite considerable annual variation in the number of cases of scarlet fever, the incidence of nephritis remained strikingly close to the mean value for the fifteen years, namely, 2.62 per cent. The cases of nephritis were about equally divided between males and females; the age incidence of nephritis followed approximately the age incidence of the infection itself. Patients suffering from recurrent attacks of scarlet fever exhibited a considerably greater predisposition to nephritis; the incidence in these persons amounted to 16 per cent. The immediate mortality from postscarlatinal nephritis was 1 per cent. Of 295 patients with nephritis discharged from the hospital, 232 (78 per cent) were reexamined at varying intervals of years after the original attack of nephritis; 13 (6 per cent) showed evidence of more or less severe chronic nephritis (of these, 2 died in uremia); 10 who had not yet attained puberty had signs of mild nephritis. This group of 23 subjects amounts to 10 per cent of the follow-up material. In addition, 10 patients manifested hypertension and enlargement of the heart without evidence of renal irritation. In 38 cases (16 per cent) a history was obtained of one or more recurrences of nephritis since the original illness; in only 10 of these cases did an acute infection appear to have precipitated the recurrence. In 10 cases orthostatic albuminuria was detected.

The author's statistics are contrasted with those of Petrén, who carried out a comparable study with reference to 7,140 cases of scarlet fever in Malmö, Sweden. Although Petrén's figure for the immediate mortality from nephritis (3.9 per cent)

is more ominous, he demonstrated chronic nephritis in only about 1.5 per cent of 254 patients whom he examined several years after the original attack of post-scarlatinal nephritis.

The bibliography contains 60 titles. The protocols of 57 cases are included.

McCUNE, New York.

## Acute Infectious Diseases

AMEBIC DYSENTERY IN NORTH CAROLINA. J. M. RUFFIN, Am. J. Digest. Dis. **5**:153 (May) 1938.

Fifty-four cases of amebic dysentery form the basis of this report. These cases were seen in Duke Hospital, Durham, N. C. The report tends to show that amebic dysentery is prevalent in North Carolina and stresses the importance of proctoscopic examination. Adequate treatment is highly effective in amebic dysentery.

MORRISON, Savannah, Ga.

ON THE EFFECTIVENESS OF CARBARSONE AS A REMEDY FOR AMOEBIASIS. E. G. HAKANSSON, Am. J. Trop. Med. **18**:245 (May) 1938.

Hakansson studied the effect of carbarsone on amebiasis from the standpoint of dosage and duration of treatment. He concluded that relatively large doses over a short period were more effective than smaller ones over a longer period. Few patients showed toxic symptoms when as much as 0.25 Gm. per kilogram of body weight was given over a period of ten days.

BURPEE, Augusta, Ga.

A SEVENTH YEAR'S OBSERVATION ON MALARIA IN PANAMA. H. C. CLARK and W. H. W. KOMP, Am. J. Trop. Med. **18**:271 (May) 1938.

Clark and Komp report on the seventh year of their study of malaria in Panama. They are attempting to get rid of malaria in certain regions of Panama by destroying the "seed bed" of malaria which exists in young children and adolescents by using antimalarial drugs such as quinine sulfate, atabrine and plasmochin. They conclude that there is little hope of destroying this "seed bed" because of two factors: the impossibility of treating all carriers adequately and the relative inefficiency of the drugs used.

BURPEE, Augusta, Ga.

OBSERVATIONS CONCERNING THE TOXICITY, ABSORPTION AND THERAPEUTIC EFFECT OF SULPHANILAMIDE AND CERTAIN RELATED ORGANIC SULPHUR-CONTAINING COMPOUNDS IN EXPERIMENTAL INFECTIONS IN MICE. W. H. FEINSTONE, E. A. BLISS, E. OTTE and P. H. LONG, Bull. Johns Hopkins Hosp. **62**:565 (June) 1938.

Sulfanilamide is highly effective in the treatment of experimental streptococcic infections in mice. 4,4'-diaminodiphenyl sulfone is more active in experimental streptococcic infections than is sulfanilamide but is also highly toxic for mice. Di-(acetylamino)-diphenylsulfone shows a degree of activity in experimental streptococcic infections in mice which warrants a careful clinical trial of this compound in hemolytic streptococcic infections in man. "Disulfanilamide," its dimethyl derivative, and parabenzylaminobenzene sulfonamide show a moderate degree of activity in experimental streptococcic infections in mice.

4,4'-diaminodiphenylsulfone shows therapeutic activity in experimental infections with pneumococci of types I and II. Its toxicity, in the opinion of these workers, precludes its use in human beings. Sulfanilamide, "disulfanilamide," the dimethyl derivative of "disulfanilamide," di-(acetylamino)-diphenylsulfone and parabenzylaminobenzenesulfonamide showed little or no therapeutic activity in experimental pneumococcic infections in mice.

In experimental meningococcic infections in mice, sulfanilamide, "disulfanilamide," diaminodiphenylsulfone and di-(acetylamino)-diphenylsulfone all showed about the same degree of therapeutic activity. The dimethyl derivative of "disulfanilamide" and parabenzylaminobenzene sulfonamide were definitely less active as therapeutic agents.

Sulfanilamide, "disulfanilamide" and its dimethyl derivative showed low degrees of activity in experimental staphylococcic infections in mice.

The experimental data recorded in this paper indicate that sulfanilamide is from all points of view the most suitable compound for the treatment of hemolytic streptococcic and meningococcic infections in man. It is of doubtful value in pneumococcic and staphylococcic infections.

FROM THE AUTHORS' CONCLUSIONS.

INFLUENCE OF TONSILLECTOMY UPON THE COURSE OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE: A STUDY OF 108 CASES. W. B. ALLAN and J. W. BAYLOR, Bull. Johns Hopkins Hosp. **63**:111 (Aug.) 1938.

A group of 108 patients who were subjected to tonsillectomy and adenoidectomy because of rheumatic fever between 1910 and 1924 were reinvestigated in 1935. The object was to determine the effect of this operation on (1) the incidence of recrudescences of rheumatic fever and (2) the appearance or progression of rheumatic heart disease in subjects known to be rheumatic. The average age of the 86 living patients was 26.4 years. It is noted that while rheumatic fever is as common in Baltimore as in Boston the character of the disease and the acute manifestations are milder in Baltimore than in other localities.

The incidence of cardiac involvement in the group was low, and the authors conclude that since rheumatic heart disease developed in only 6 of 49 rheumatic patients not having cardiac involvement at the time of operation, tonsillectomy and adenoidectomy are to be recommended in the treatment of rheumatic fever.

The study also showed that: 1. Following operation, recrudescences of acute rheumatic manifestations occurred in 43.5 per cent of the patients. 2. Recrudescences were common in the first five years after operation. Most of the patients who had repeated recrudescences during this period died of rheumatic heart disease. 3. Patients living for more than five years after operation had almost as many recrudescences after the fifth year period as during it. 4. Evidence of continued nasopharyngeal infection was prominent in the patients having recrudescences.

LYTTLE, New York.

THE SYMPTOMS, DIAGNOSIS AND TREATMENT OF UNDULANT FEVER. J. G. CARR, Illinois M. J. **73**:521 (June) 1938.

Carr reviews the literature and comments on the symptoms, diagnosis and treatment of undulant fever. The article is too comprehensive to be satisfactorily abstracted.

BARBOUR, Peoria, Ill.

VITAMIN C EXCRETION IN CHILDREN, WITH PARTICULAR REFERENCE TO RHEUMATIC FEVER. J. D. KEITH and E. M. HICKMANS, Arch. Dis. Childhood **13**:125 (June) 1938.

Keith and Hickmans carried out an investigation on several groups of children with and without infection in an attempt to estimate the value of a biochemical test for vitamin C in the urine, with a view to the use of this test as an indication of various degrees of vitamin C deficiency. They discuss the limits of the value of this test in determining the various stages of healing in patients with scurvy. A group of 39 children between the ages of 2 and 13 years in the medical and surgical wards of the hospital who had little or no evidence of infection were found to excrete, on the average, daily, 9.7 mg. of ascorbic acid in

the urine. The older age group (from 7 to 13 years) was found to excrete daily 11.5 mg., and the younger group (from 2 to 6 years), 5.5 mg. Marked individual variations were noted. Children with acutely active rheumatic fever excreted more vitamin C than convalescent ones. The convalescent rheumatic patients excreted an amount approximately the same as the controls in a similar age group. Saturation tests revealed a slight deficiency in the stores of the vitamin in patients with active rheumatic fever as compared with convalescent rheumatic patients or controls. The administration of sodium salicylate (50 grains [0.3 Gm.]) and sodium bicarbonate (100 grains [6.5 Gm.]) was found to increase the excretion of vitamin C in the urine. Fever induced by the use of typhoid vaccine produced a slight increase in the excretion of vitamin C. No direct evidence was found to support the theory that rheumatic fever is a manifestation of a deficiency of vitamin C associated with an infection.

KELLY, Milwaukee.

OUTBREAK OF SONNE DYSENTERY DUE TO CONSUMPTION OF MILK. G. K. BOWLES, Brit. M. J. **1**:1092 (May 21) 1938.

An outbreak of Sonne dysentery due to drinking contaminated milk is described. Fifty-nine of 106 households and 96 among 224 persons (estimated) were affected. The period of incubation was usually from twelve to twenty-four hours. The symptoms as a rule lasted from twelve to thirty-six hours. Sonne dysentery bacilli were isolated from the feces of some of the patients and from the milk itself. The actual source of the bacilli in the milk remains untraced.

ROYSTER, University, Va.

ACUTE ARTICULAR RHEUMATISM IN CHILDHOOD. F. THOENES, Med. Klin. **34**: 245 (Feb. 25) 1938.

Nothing definitely new is presented regarding the causes and nature of acute articular rheumatism in children. In treatment Thoenes prefers aminopyrine to salicylates. He discusses general measures in management, advocating prolonged rest and a diet low in calories. He also considers proper treatment of the nose and throat important. The sedimentation rate is considered a valuable guide in regard to rheumatic activity.

SIEMSEN, Chicago.

OCULAR CHANGES IN WEIL'S DISEASE. M. S. KOSTER, Nederl. tijdschr. v. geneesk. **82**:1577 (April 2) 1938.

In an adult patient suffering from Weil's disease a number of ocular changes were seen, among which was a form of corneal edema, interpreted as keratitis parenchymatosa. Intramuscular injections of milk gave complete healing.

VAN CREVELD, Amsterdam, Netherlands.

## Chronic Infectious Diseases

TUBERCULOSIS OF CERVICAL LYMPH NODES. B. C. THOMPSON, Am. Rev. Tuberc. **37**:410 (April) 1938.

Five thousand patients were studied in an attempt to determine the incidence of subclinical tuberculosis of the peripheral lymph nodes and of manifest tuberculous adenitis and the relationship between tuberculous adenitis and pulmonary tuberculosis. It was found that the incidence of tuberculous cervical adenitis, active and obsolete, was approximately the same as was found in 1,000 patients admitted in 1907, i. e., 1.80 per cent in the earlier patients and 1.02 per cent in patients admitted during the years from 1933 to 1937.

Associated intrathoracic tuberculosis was found in patients with tuberculosis of the supraclavicular and axillary groups of lymph nodes but not in patients in

whom the upper deep cervical lymph nodes alone were involved. It appears, therefore, that patients of the former group were infected primarily by a pulmonary route and the latter primarily by a nasopharyngeal route.

EUGENE H. SMITH, Ogden, Utah.

INFLUENCE OF SUNLIGHT UPON EXPERIMENTAL TUBERCULOSIS. A. C. UKIL and S. R. GUHA THAKURTHA, Am. Rev. Tuberc. **37**:448 (April) 1938.

The authors undertook this study of the biologic influence of sun rays on animals in India in an effort to determine the part played by open air and sunshine on tuberculous infection and disease. They had noted that while positive reactions to tuberculin occurred with about the same frequency in boys and girls of the ages between 6 and 10 years, a rapid increase in positive reactions was found in girls above the age of 10 years. In females between 16 and 20 years of age the incidence arose to double that of males. This corresponds to the age at which girls begin to observe purdah (partial seclusion at home), with consequent more or less deprivation of fresh air and sunlight. Their experiments were made with guinea pigs inoculated with human tubercle bacilli and with healthy controls, under four conditions: (1) in a well ventilated room in the shade; (2) exposed to direct sunlight; (3) exposed to sunlight filtered through glass admitting rays up to 2,910 angstroms while cutting off nearly 90 per cent of the heat rays, and (4) in open enclosures with free access to sunshine and shade. It was found that the animals confined in cages sustained a greater loss of weight and had a shorter survival period than those enjoying freedom of movement. However, the animals exposed to filtered rays of sunlight showed greater resistance to the evolution and extension of disease in the viscera than the other groups. The survival period of animals which were allowed freedom of movement was longest, but these animals also showed more extensive disease. A factor which the investigators were unable to overcome in their experiments was the unfavorable influence of heat rays, direct and radiated. They concluded that if solar radiations are to be utilized for therapeutic purposes in India some method of counteracting the deleterious influence of heat rays must be found.

EUGENE H. SMITH, Ogden, Utah.

VARIABILITY OF FINDINGS IN TUBERCULOUS MENINGITIS. H. E. THELANDER and J. BALDWIN, Arch. Pediat. **55**:225 (April) 1938.

The variability of symptoms and physical findings in 135 cases of tuberculous meningitis is outlined.

TABLE 1.—*Symptoms Given in Histories in 135 Cases*

| | | Cases |
|---|---|---|
| 1. | Vomiting | 79 |
| 2. | Fever | 71 |
| 3. | Headache | 46 |
| 4. | Anorexia | 31 |
| 5. | Lassitude | 27 |
| 6. | Irritability | 27 |
| 7. | Cough and cold | 20 |
| 8. | Constipation | 17 |
| 9. | Loss of weight | 14 |
| 10. | Convulsions | 5 |
| 11. | Vertigo | 5 |
| 12. | Twitching | 5 |
| 13. | Photophobia | 5 |
| 14. | Drowsiness | 4 |
| 15. | Pain in neck, diplopia, unconsciousness, each | 1 |
| 16. | Strabismus, unilateral weakness, spasticity, each | 1 |

TABLE 2.—*Findings on Examination in 135 Cases*

| | Cases |
|---|---|
| 1. Fever (all cases) | 135 |
| 2. Stiffness of neck (definite) | 94 |
| 3. Kernig sign | 54 |
| 4. Unconsciousness on admission | 47 |
| 5. Convulsions | 30 |
| 6. Emaciation | 33 |
| 7. Paralysis | |
| Strabismus | 30 |
| Facial paralysis | 15 |
| Hemiplegia | 10 |
| Ptosis | 9 |
| Inequality of pupils | 8 |
| Paralysis of arm | 3 |
| 8. Often a palpable spleen | |
| 9. Involvement of chest | |
| (a) Negative findings | 104 |
| (b) Dulness and changed breath sounds | 12 |
| (c) Diffuse râles | 10 |
| (d) Localized râles | 6 |
| (e) Bronchopneumonia | 2 |
| (f) Effusion | 1 |

The tubercle bacillus was recovered in 62 per cent of the spinal fluids examined.

ORR, Buffalo.

ENDOCRINE DEFICIENCY IN SYPHILIS. H. HOSEN, New Orleans M. & S. J. **90**: 707 (June) 1938.

Hosen reports 3 cases of syphilis in which there was associated mental deficiency. Antisyphilitic treatment effected no change in the mental status. Roentgen study of the epiphysial development revealed retarded skeletal growth, indicating thyroid insufficiency. The addition of thyroid treatment to the antisyphilitic treatment produced marked improvement in the mental status in each case.

BERKLEY, Los Angeles.

TUBERCULOSIS CASE FINDING AMONG CHILDREN. W. J. RYAN, New York State J. Med. **38**:494 (April 1) 1938.

The Mantoux test, with 0.5 mg. of old tuberculin, was made on 10,033 school children. Forty-five per cent gave positive reactions and were submitted to roentgen examination. One per cent showed manifest disease and 4.8 per cent healed lesions of the childhood type. In a group of 1,091 children who had been in contact with tuberculous patients 139 were found to have positive indications of infection by roentgenogram. While the method of testing with tuberculin and examining by means of roentgenograms is of great value, more stress must be placed on a study of the group who are known to have contact with tuberculous patients.

AIKMAN, Rochester, N. Y.

TUBERCULIN-TEST OF SCHOOL CHILDREN (COMPARATIVE VALUES). G. W. WEBER, F. W. HOLCOMB and K. M. MURPHY, New York State J. Med. **38**:685 (May 1) 1938.

School children of all ages were given tuberculin tests and fluoroscopic and roentgen examinations as a means of detecting active tuberculosis in persons in their homes. This method was found more expensive and generally less satisfactory than clinical examinations of members of the households of children known to have tuberculosis and of those with suspicious symptoms as a method of detecting adults with the disease. The former method was, however, of great educational value to the children.

AIKMAN, Rochester, N. Y.

CONGENITAL SYPHILIS IN NATIVE AND CHINESE INFANTS IN BATAVIA. W. DE JONG-MARTIS, Indian J. Pediat. **5**:53 (April) 1938.

Following a study of 105 congenitally syphilitic infants and 10 syphilitic children over 1 year of age, the author observes, among other things, that: (1) bullous syphilid at birth was not seen at all; (2) snuffles occurred in 57 per cent of the infants; (3) condylomas occurred in 10; (4) enlarged cranial veins were found in 25; (5) the spleen was not palpable in 57; (6) symptoms and signs of neurosyphilis could not be demonstrated in a single infant; (7) roentgen evidence of periostitis was present in 91 of 94 infants, it being the only change in 36; (8) roentgen evidence of epiphysiolysis could not be demonstrated in 8 infants showing pseudoparalysis; (9) serologic tests of blood from the umbilical cord had no practical value for an early diagnosis of congenital syphilis.

GONCE, Madison, Wis.

STATISTICAL AND CLINICAL DATA ON CONGENITAL SYPHILIS AMONG ILLEGITIMATE INFANTS. G. SORGE, Méd. inf. **9**:46 (Feb.) 1938.

The data on which the article is based were gathered from the provincial orphanage at Catania, Italy. Congenital syphilis was present in 35, or 1.6 per cent, of the 2,200 children admitted to the orphanage in the past three years. Three of the syphilitic infants were premature; 27.5 per cent of the congenital syphilitic infants and 2.5 per cent of the normal infants had palpable epitrochlear glands, while 73 per cent of the syphilitic and 13 per cent of the nonsyphilitic infants had palpable spleens. The Wassermann reaction was negative in 6 instances, doubtful in 9 and positive in 14. One case is noted in which the Wassermann reaction of the mother's blood was negative and that of the child's blood positive, and another in which the reaction of the mother's blood was positive and that of the child's blood negative. In the 12 syphilitic children who were nursed by their mothers, there was a mortality of 25 per cent; 8 infants were fed by syphilitic wetnurses, with a mortality of 50 per cent, and 13 infants were artificially fed, with a mortality of 92 per cent.

HIGGINS, Boston.

CLINICAL SIGNIFICANCE AND SOCIAL IMPORTANCE OF PERIFOCAL INFILTRATION IN CHILDREN. G. ACQUAFREDDA, Méd. inf. **9**:65 (March) 1938.

Perifocal infiltration was diagnosed in 34 of 310 children with positive reactions to tuberculin. The perifocal infiltration may occur in three forms: (1) perihilar, (2) interlobar and (3) pleuritic. Roentgen examination is necessary for accurate diagnosis.

HIGGINS, Boston.

EARLY DIAGNOSIS OF TUBERCULOSIS IN THE INFANT. F. DE NICOLO, Lattante **9**:55 (Feb.) 1938.

De Nicolo reviews the literature on the diagnosis, prognosis and treatment of tuberculosis in infancy.

HIGGINS, Boston.

SYPHILIS IN THE MOTHER. M. MONACELLI, Lattante **9**:207 (May) 1938.

This is a review of the literature on maternal syphilis.

HIGGINS, Boston.

SEDIMENTATION RATE OF THE BLOOD IN SOME DISEASES OF CHILDREN, ESPECIALLY IN "PRETUBERCULOSIS." G. VANNI, Riv. di clin. pediat. **36**:397 (May) 1938.

Pretuberculosis is an early phase of tuberculosis, with the infectious agent in the protogenic, or virus, stage; the lymph glands are affected, and the tuberculin test is negative (Fiore: AM. J. DIS. CHILD. **50**:1282 [Nov.] 1935).

The sedimentation rate was normal in 10 of 12 cases of "pretuberculosis." In 11 cases of adenitis, similar clinically but with the tuberculin reaction positive,

the sedimentation rate was normal. In 7 cases of more extensive and severe tuberculosis the sedimentation rate was increased.

A marked increase in the sedimentation rate was found in cases of malignant lymphogranuloma and a small increase in cases of subacute respiratory infections—bronchopneumonia, asthma, bronchiectasis.

HIGGINS, Boston.

TUBERCULOUS PERITONITIS IN AN INFANT OF EIGHTEEN MONTHS. M. S. S. DE RODRIGUEZ and J. M. ABDALA, Arch. de pediat. d. Uruguay **9**:292 (May) 1938.

The authors present the case of an 18 month old girl who from the age of 4 months on had repeated attacks of bronchitis and had a history of contact with a tuberculous grandfather and a tuberculous neighbor. Ascites developed. The child recovered. The treatment consisted in repeated abdominal taps, rest, ultraviolet irradiations and injections of irradiated calcium. The diagnosis of tuberculous peritonitis was made from the positive reaction to tuberculin, the history of contact, the nature of the peritoneal fluid and the favorable reaction to treatment.

SCHLUTZ, Chicago.

SOME CASES OF CONGENITAL SYPHILIS IN THE NETHERLAND EAST INDIES. W. DE JONG-MARTIS, Maandschr. v. kindergeneesk. **7**:193 (Feb.) 1938.

Contrary to former opinions, congenital syphilis occurs frequently among the native and the Chinese infants in the Netherland East Indies. The author has observed about 150 cases. Although the disease in most cases manifested itself in the classic manner, almost every congenitally syphilitic child also showed one or more particular symptoms, of which a few are described.

VAN CREVELD, Amsterdam, Netherlands.

RELIABILITY OF THE INOCULATION AND CULTURAL METHOD IN THE SEARCH FOR TUBERCLE BACILLI. A. C. RUYS, Nederl. tijdschr. v. geneesk. **82**:18 (Jan. 1) 1938.

For the isolation of tubercle bacilli from urine, pus and spinal fluid, the cultural method is almost as reliable as that of the inoculation of guinea pigs, with the human as well as with the bovine type. For the demonstration of tubercle bacilli by gastric lavage, the material should be centrifuged and the deposit injected into guinea pigs without preliminary treatment. The omission of the treatment with acid or alkali increases the number of positive results. So, for the demonstration in gastric lavage of not only the bovine but also the human type, the animal experiment is more reliable than the cultural method, which always needs the damaging preliminary treatment. In examining sputums that are microscopically negative both methods should be used, because each of them fails from time to time.

VAN CREVELD, Amsterdam, Netherlands.

LIME DEPOSITS IN THE LUNGS AND THE COURSE OF TUBERCULOSIS OF THE LUNGS. J. H. REICHART, Nederl. tijdschr. v. geneesk. **82**:3065 (June 18) 1938.

This is a consideration of some conspicuous occurrences in the course of tuberculosis of the lungs, characteristic for childhood phases I and II of the scheme of the German pathologist Ranke, more especially of the significance of lime deposits and bone formation. Reichart records the case of an adult whose tuberculosis did not belong to these two phases in whom during life these two phenomena (deposition of lime and bone formation) were observed. He is inclined to think that the conversion of tuberculous areas into stonelike material occurs more frequently in adults than is generally admitted.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Blood, Heart and Blood Vessels and Spleen

LEUKEMIAS OF INFANCY AND EARLY CHILDHOOD. H. A. SPIGEL, Arch. Pediat. **55**:7 (Jan.) 1938.

Spigel reviews the etiology of the leukemias. He considers each of these conditions not as a disease by itself but as secondary to a hidden infection resulting in proliferation and growth of the blast cells, which cells are hereditarily susceptible to the effects of a specific infection. By "specific infection" Spigel explains that he means an infection specific for the patient. In the presence of aleukemia, the term "aleukemic" may be added to the term describing any of the forms of leukemic disease. He reports 12 cases of acute lymphatic leukemia with two alleged recoveries, 2 of chronic leukemia with no recoveries and 5 of acute myelogenous leukemia with one recovery are reported.

ORR, Buffalo.

A PRELIMINARY REPORT ON A PLATELET-REDUCING SUBSTANCE IN THE SPLEEN OF THROMBOCYTOPENIC PURPURA. C. E. TROLAND and F. C. LEE, Bull. Johns Hopkins Hosp. **62**:85 (Jan.) 1938.

An extract made from the spleens of 3 patients with thrombopenic purpura was found to contain a substance which would reduce the number of platelets in the circulating blood of a normal rabbit as much as 90 per cent. Control extracts made from other organs and from the spleens of nonthrombopenic persons had no effect. Further studies are being made.

LYTTLE, New York.

FUNCTIONAL HEART MURMURS IN NEWBORN INFANTS. W. J. SIEMSEN, Illinois M. J. **72**:157 (Feb.) 1938.

Of 106 newborn infants at the Presbyterian Hospital, Chicago, 26 were found to have cardiac murmurs. The incidence varied from 12 per cent in infants examined only once to 37 per cent in infants examined three times. For various reasons the murmurs are regarded by Siemsen as functional.

BARBOUR, Peoria, Ill.

IRON METABOLISM IN EXPERIMENTAL ANEMIA: "AVAILABILITY OF IRON." P. F. HAHN and G. H. WHIPPLE, J. Exper. Med. **67**:259 (Feb.) 1938.

"The availability of iron" is a term much used in current writings, particularly in those articles dealing with various forms of anemia. The dipyridyl method for the determination of "available iron" was introduced by Hill in 1930. Hahn and Whipple set out to show that the so-called "available iron" is not all utilized by the body when taken by mouth. Numerous experiments in dogs given 40 mg. of iron by mouth per day for fourteen days (total, 560 mg. of iron) show a net production of from 50 to 55 Gm. of new hemoglobin above the control output on the basal ration. If given by vein, this same dose of iron will yield a 100 per cent return of hemoglobin, or from 160 to 170 Gm. of hemoglobin, net output; therefore this iron is 100 per cent "available," as determined by the dipyridyl method and by intravenous tests. Given by mouth, it is only about 35 per cent "available." The term "available iron" simmers down to iron not in the form of a hemoglobin compound. The absorption of this "available iron" is conditioned by a great variety of factors, many unknown at this time.

KNICKERBOCKER, Dallas, Texas.

TRANSFUSIONS. L. N. SUSSMAN, New York State J. Med. **38**:264 (Feb. 15) 1938.

Repeated small transfusions were given to two children to offset postoperative drops in hemoglobin and in nutrition.

AIKMAN, Rochester.

FAT METABOLISM OF THE ISOLATED HEART. M. B. VISSCHER, Proc. Soc. Exper. Biol. & Med. **38**:323 (April) 1938.

The combustion of fat has been suspected of supplying a part of the energy used by the isolated heart. Analyses for total fats were made of the heart muscle of 63 hearts, 25 of which had been worked for from one to six hours in the heart-lung apparatus. The mean difference in the total fats was 0.53 per cent of wet weight with a probable error of the difference of ± 0.123, a statistical difference. Thus it would appear that fat is utilized by the actively metabolic heart muscle.

HANSEN, Minneapolis.

PHOSPHORUS FRACTIONS IN HUMAN HEART MUSCLE. G. M. DECHERD JR. and J. E. BLUM JR., Proc. Soc. Exper. Biol. & Med. **38**:341 (April) 1938.

It has been shown that there is a decrease in the total phosphorus of muscle in myocardial failure. Muscle was taken from the left ventricles in 36 normal hearts from human subjects and 33 hearts from persons who died of cardiac failure. Analyses revealed that the decrease in the total phosphorus was in acid-soluble phosphorus compounds.

HANSEN, Minneapolis.

FAMILIAL IDIOPATHIC METHAEMOGLOBINAEMIA. E. H. BENSLEY, L. J. RHEA and E. S. MILLS, Quart. J. Med. **7**:325 (April) 1938.

The authors describe familial methemoglobinemia occurring in a brother and sister, aged 37 and 43 years, respectively. In each instance the cyanosis was first noted at 11 years of age. Methemoglobinemia is classified according to the following etiologic factors: (*a*) poisons, (*b*) hemolytic processes, (*c*) enterogenous factors giving rise to cyanosis and (*d*) idiopathic conditions. The various forms are described.

BRADFORD, Rochester, N. Y.

VEGETATIVE INTIMITIS OF THE PULMONARY ARTERY IN A BOY WITH CONGENITAL INTRAVENTRICULAR SEPTAL DEFECT, PERSISTENT CONUS ARTERIOSUS AND BICUSPID PULMONARY VALVE. L. C. POSEY, South. M. J. **31**:761 (July) 1938.

Posey reports this condition in an 8 year old white boy. The process terminated fatally. The autopsy uncovered a basal defect of the interventricular septum with congenital constriction of the conus arteriosus and bicuspid pulmonary valves. Massive infectious endocarditis of the pulmonary valves and endarteritis of the pulmonary artery had been produced by Streptococcus viridans.

The lungs contained numerous mycotic emboli. The right ventricle of the heart was greatly hypertrophied, and the pulmonary artery was slightly dilated.

Posey believes that the localization of infection in this case can be explained on the basis of the sclerosis due to increased pulmonary arterial tension.

SCHLUTZ, Chicago.

A CASE OF PERIARTERITIS NODOSA WITH SUBCUTANEOUS LESIONS AND RECOVERY. C. W. VINING, Arch. Dis. Childhood **13**:31 (March) 1938.

A 7 year old girl who had acute rheumatic fever and periarteritis nodosa recovered. Biopsy of one of the nodes revealed the characteristic changes.

KELLY, Milwaukee.

GAUCHER'S DISEASE IN CHILDREN. F. R. B. ATKINSON, Brit. J. Child. Dis. **35**: 1 (Jan.-March) 1938.

The article consists of a short historical review followed by a tabulation of 108 instances in children compiled from the literature. The disease occurred about equally in the two sexes. In about 50 per cent of the instances there was a familial history. The symptomatology and the blood changes are reviewed.

It is now generally believed that the disease is familial, that it affects the reticular cells of the lymphatic and hemopoietic system and that it is due to a disturbance of the metabolism of lipoids, especially the cerebrosides, so that kerasin is deposited in large quantities in the reticular cells of the aforementioned systems.

The progress is much more rapid in children than in adults; 40 of the 108 children died before the age of 12 years. LANGMANN, New York.

CHRONIC NUTRITIONAL HYPOCHROMIC ANAEMIA. L. S. P. DAVIDSON and H. W. FULLERTON, Edinburgh M. J. **45**:193 (March) 1938.

This is part III of the authors' consideration of the subject and deals with treatment. Two of the 20 pages concern the treatment of infants for chronic nutritional hypochromic anemia. The remaining pages are devoted to the treatment of adults.

All children with a low weight at birth need iron from the second month of life. After an infection iron should be given for weeks, since even mild infections result in anemia and retard regeneration of blood. It should be given to any infant who is pale, fatigued and not thriving.

The dosage for an infant of from 3 to 6 months of age is 1½ grains (0.096 Gm.) of iron and ammonium citrate three times daily, and double this amount if anemia is already present. The latter dosage is used as a prophylactic in older infants, from 6 to 18 months old, and from 5 to 10 grains (0.32 to 0.65 Gm.) as curative.

Ferrous sulfate is the preferable salt, as it permits smaller doses than the citrate and should be prescribed in 50 per cent dextrose to retard oxidation of the iron to the ferric state.

It is advisable to begin medication with from one third to one half of the optimal dose so that digestion may not be deranged. NEFF, Kansas City, Mo.

ANEMIA OF PREGNANCY. C. ORAZIO, Méd. inf. **9**:111 (April) 1938.

A woman in the sixth month of pregnancy was admitted to the hospital in Messina, Sicily, because of anemia. The hemoglobin content of the blood was 25 per cent; the red cell count, 1,200,000; the white cell count, 4,500. None of the usual causes of anemia could be found, such as syphilis, malaria, parasitic infestation or hemorrhage. After twenty days' treatment the anemia had not improved. On the twenty-fourth day after admission the patient suffered a spontaneous abortion. Immediately following this the red cell count and the hemoglobin content began to return to normal so that one month later the hemoglobin content was 75 per cent and the red cell count 3,800,000.

HIGGINS, Boston.

ACUTE PERICARDITIS IN AN INFANT. B. SANCHEZ SANTIAGO, Bol. Soc. cubana de pediat. **10**:387 (July) 1938.

A 3 month old infant presented marked cardiovascular signs. In the absence of pulmonary signs a diagnosis of acute pericarditis was made, which was confirmed by fluoroscopic observation, roentgenograms and pneumopericardium. At autopsy the observations were acute pericarditis and hilar bronchopneumonia, both of staphylococcic origin. SCHLUTZ, Chicago.

CLINICAL AND CHEMICAL OBSERVATIONS IN GAUCHER'S DISEASE. M. ZEHNDER and LEUTHARD, Deutsche Ztschr. f. Chir. **250**:423, 1938.

Gaucher's disease is classed with Niemann-Pick disease and Schüller-Christian disease as a familial constitutional disturbance of lipoid metabolism with respect to the reticuloendothelial system. In Gaucher's disease a cerebroside, kerasin, is

found in the reticuloendothelial cells; in Niemann-Pick disease a phosphatide, and in Schüller-Christian disease, cholesterol.

In the past ten years in the University Clinic, Zurich, Switzerland, three cases of Gaucher's disease have been observed.

CASE 1.—A girl born of Gentile parents with no family history of splenic disease was distinguished from her two younger sisters by the facts that she was always more delicate, always had difficulty with her bowels and had a craving for fatty foods, especially butter and cheese. At the age of 1 year she was noted by the mother to have a large spleen but was not brought to the clinic until she was 6 years of age. At that time Banti's disease, Gaucher's disease and thrombosis of the splenic vein were considered. At the age of 10 years a diagnosis of Gaucher's disease was established by sternal puncture. A roentgenogram of the lungs showed a marked increase in markings, which was attributed to infiltration with Gaucher's cells. At operation the spleen measured 22.5 by 121.5 by 6 cm. and weighed 1,200 Gm. The child recovered uneventfully from the operation.

CASE 2.—A Jewish boy underwent splenectomy at 13 years of age and two years later had to undergo another operation because of enlargement of an accessory spleen with the same disease. Previous to operation there was an unsuccessful attempt to shrink the spleen by roentgen therapy.

CASE 3.—A Jewish woman 32 years of age had had a large spleen at least since the age of 4 years. At the age of 21 years she had an attack of severe abdominal pain, which was attributed to twisting of the spleen on its pedicle. At the age of 23 years she had a normal pregnancy and delivery. It is interesting that she had never felt better than during this pregnancy. The spleen was removed at the age of 32 years after a sternal puncture had confirmed the diagnosis of Gaucher's disease. A roentgenogram of the femurs showed osteoporosis of the distal ends. This is said to be a favored site for Gaucher cell infiltration of the bones.

The case reports are well illustrated and contain many interesting details of great importance to a student of this disease, relating to the blood pictures, chemical studies and pathologic studies—too many to be conveniently abstracted. In summing up, the authors emphasize the importance of sternal puncture in the diagnosis of the disease, its superiority to biopsy of a lymph node and its safety as compared with splenic puncture. They recommend that the sternal puncture be used in every case of splenomegaly of unknown origin. The possible relationship of the adrenal cortex to the lipoid metabolism of the reticuloendothelial system in this disease is also discussed.

GLASER, Rochester, N. Y.

THE NORMAL THROMBOCYTE PICTURE IN INFANTS. J. ARNETH, Monatschr. f. Kinderh. **73**:34 (April) 1938.

The platelet count diminishes from roughly 250,000 per cubic millimeter at birth to 228,000 at the end of the first week. In the second week the count is 412,000, in the third week 396,000 and from the fourth to the twenty-sixth week 409,000. From then to the end of the year it averages 344,000.

The platelets are of two types: round to oval forms (right) and rod forms (left). The infant's platelet count shows a characteristic shift to the left during the first year.

Arneth believes that these counts should be taken into consideration and that they may become as important in diagnosing infectious and toxic processes as the leukocyte count.

GERSTLEY, Chicago.

THE LEUKOCYTE COUNT IN CHILDREN. J. ARNETH, Monatschr. f. Kinderh. **73**:115 (April) 1938.

The leukocyte count during the first postnatal days averages about 20,000 per cubic millimeter. During the first four weeks after birth it ranges between 10,000 and 20,000, and by the end of the first year it drops below 10,000. Neutrophils, which predominate in premature infants, begin to diminish at birth, after which lymphocytes predominate. During the first three months of life there is a shift to the left.

Eosinophils and mast cells react generally as do neutrophils. Eosinophils are slightly increased in the newborn.

The lymphocytic count shows a great preponderance of small lymphocytes. The medium and large lymphocytes shift to the right. GERSTLEY, Chicago.

ALLERGIC PURPURA. A. VAN WESTRIENEN, Maandschr. v. kindergeneesk. **7**:297 (May) 1938.

Westrienen describes Henoch's purpura in a boy of 3 years with intestinal and various cutaneous hemorrhages, which appeared after the use of different food substances: animal protein, oranges, lemons, tomatoes, potatoes and marrow peas. After keeping to a strict but sufficient diet, the child showed a greatly improved condition and permanent cessation of the hemorrhages.

VAN CREVELD, Amsterdam, Netherlands.

A SMALL APPARATUS FOR THE DETERMINATION OF THE MEAN DIAMETER OF THE RED BLOOD CORPUSCLES. L. SCHALM, Nederl. tijdschr. v. geneesk. **82**:1817 (April 16) 1938.

A simple apparatus in pocket size is described for determining the mean diameter of erythrocytes by the diffraction method. It has the advantages of its small size (about 2 by 6 cm.) and of being usable with any kind of light. It is intended for bedside practice. VAN CREVELD, Amsterdam, Netherlands.

DETERMINATION OF THE DIAMETER OF THE RED CORPUSCLES BY MEANS OF PYPER'S METHOD. E. P. SNYDERS and T. K. BOK, Nederl. tijdschr. v. geneesk. **82**: 2018 (April 23) 1938.

Snyders and Bok discuss the diffraction method for the measurement of the mean erythrocyte diameter and compare the values obtained by means of the blood cell tester of Pyper with those obtained by an exact direct method. They conclude: 1. The values of the mean erythrocyte diameter obtained by Pyper's method are in good accordance with those resulting from the measurement of from 500 to 1,000 cells. This holds true for normal blood as well as for microcytoses and macrocytoses (at least between 6.6 and 9.2 microns). Siedentopf's formula, $\frac{395}{D \cdot 1}$ (in which D is the diameter in millimeters of the outer circumference of the yellow ring of the second spectrum), fulfils its purpose very well. 2. Fixation and staining have no important influence on the diameter of the red cell.

VAN CREVELD, Amsterdam, Netherlands.

PHOSPHATIDE LIPOIDOSIS. P. H. TEUNISSEN and A. DEN OUDEN, Nederl. tijdschr. v. geneesk. **82**:2406 (May 14) 1938.

After comparing the method of Epstein and Lorenz with that of Klenk, the authors conclude that the first method does not give separate values for lecithin and sphingomyelin; the latter is more satisfactory in this respect, though with this method the separation of both substances is not an ideal one. In Niemann-Pick disease, principally, the sphingomyelin is accumulated in the spleen (from 1 per cent normally to 22 per cent), and the lecithin is only slightly increased (from 4.1 per cent normally to 7.6 per cent).

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Nose, Throat and Ear

NASOPHARYNGEAL FIBROMA: REPORT OF A CASE IN WHICH A SURGICAL APPROACH WAS EMPLOYED. R. F. NELSON, Arch. Otolaryng. **27**:313 (March) 1938.

Nelson reports the case of a 9 year old boy, stating that in this particular instance coagulation or galvanism would have been dangerous because of the proximity of the major arterial branches. Sewell's transantral approach gave access to the pterygopalatine fossa, making possible the execution there of surgical procedures with complete observance of surgical principles, including maintenance of free visibility, orientation by identification of structures and landmarks, hemostasis by ligature and avoidance of all deformity or loss of function.

GREENWOOD, Chicago.

ROLE OF THE HYPOPHYSIS IN CRANIAL OSTEOMYELITIS, PETROSITIS AND SINUS INFECTIONS. G. LEVENE, L. F. JOHNSON, R. M. LOWMAN and E. G. WISSING, Endocrinology **22**:521 (May) 1938.

In an attempt to explain why infections of the sinuses or of the mastoids sometimes spread to produce osteomyelitis of the frontal bone or suppuration of the petrous portion of the temporal bone, studies were made of roentgenograms of over 6,000 skulls.

These were divided into groups depending on the bone structure. Expansion of the trabecular network of bone, with thinning of the inner and outer tables and hyperpneumatization of the sinuses and mastoids, is interpreted as evidence of hyperactivity of the anterior lobe of the pituitary. Thin, dense bone, with poorly pneumatized sinuses, is found in patients with underactivity of the anterior lobe of the pituitary—for instance, in "pituitary dwarfs."

It was found that the incidence of sinus infection is greater in persons whose skulls show evidence of pituitary dysfunction than in persons whose skulls are normal. The importance of endocrine factors in the development and progress of these conditions is suggested.

JACOBSEN, Buffalo.

MANAGEMENT OF THE SEPTIC PATIENT WITH OTITIS MEDIA. J. H. MAXWELL, J. A. M. A. **110**:1536 (May 7) 1938.

Maxwell divides the patients into three groups: (1) those with sepsis antedating the otitis media, (2) those with sepsis originating from another source and (3) those with sepsis secondary to otitis media. He outlines the procedures necessary to arrive at a diagnosis, to determine the proper course of treatment, to carry out the correct surgical procedures and to observe postoperative developments. Mention is made of the value of sulfanilamide therapy.

HEERSMA, Kalamazoo, Mich.

LUNG ABSCESS FOLLOWING TONSILLECTOMY. RECOVERY. R. W. B. ELLIS, Proc. Roy. Soc. Med. **31**:772 (May) 1938.

In a boy of 8 years tonsillectomy was followed by a pulmonary abscess. The results of physical and roentgenologic examinations, with notes on the patient's progress, are given in this report.

WILLIAMSON, New Orleans.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

DERMOID CYSTS OF THE MESENTERY. G. C. PENBERTHY and K. M. BROWNSON, Ann. Surg. **107**:566 (April) 1938.

Only 14 cases of dermoid cysts of the mesentery proved to be such have been reported in the literature. Penberthy and Brownson report in detail an addi-

tional case in a girl aged 2, the youngest subject reported as having such a tumor.

The signs and symptoms of a dermoid of the mesentery do not differ in any respect from those of other mesenteric tumors. There are no cardinal symptoms, all complaints resulting from purely mechanical disturbances.

An exact diagnosis can be made only after celiotomy and subsequent microscopic examination of the cyst wall.

Treatment is entirely surgical. Simple enucleation is done, if possible, but if the tumor is of such size that its enucleation would embarrass the blood supply to the intestine, resection becomes necessary.

BANTIN, Omaha.

INGESTED FOREIGN BODY IN THE GASTRO-INTESTINAL TRACT. F. F. HENDERSON and E. A. GASTON, Arch. Surg. **36**:66 (Jan.) 1938.

This study was made of cases in which a foreign body or the complications arising from it were located below the esophagus and above the rectum. It was determined by the authors that an ingested foreign body that passes in natural ways usually does so within seven days, regardless of the age of the patient or the type of the foreign body. An ingested foreign body that perforates the gastrointestinal tract may do so at any point along the tract. The stomach seems to be perforated about twice as frequently as any other portion. Surgical intervention for an impacted foreign body should always be immediately preceded by roentgen examination. A comment on the conservative and on the surgical treatment is given.

KAISER, Rochester, N. Y.

NONSPECIFIC MESENTERIC ADENITIS: A REPORT OF ONE HUNDRED AND FORTY CASES. W. KLEIN, Arch. Surg. **36**:571 (April) 1938.

This clinical condition is carefully described as it occurs in its various forms. Klein contends that it is possible, in spite of voluminous literature to the contrary, to make a preoperative diagnosis of mesenteric adenitis. The most important diagnostic factor on physical examination is the shifting tenderness in mesenteric adenitis. Such a symptom is not noted in appendicitis. An analysis of the case reported shows that this condition is not necessarily an accompaniment of an infection of the upper part of the respiratory tract.

KAISER, Rochester, N. Y.

COMPARISON OF BACTERIUM NECROPHORUM FROM ULCERATIVE COLITIS IN MAN WITH STRAINS ISOLATED FROM ANIMALS. G. M. DACK, L. R. DRAGSTEDT, R. JOHNSON and N. B. MCCULLOUGH, J. Infect. Dis. **62**:169 (March-April) 1938.

The authors have made a study of 42 strains of nonsporulating gram-negative anaerobes which they call Bacterium necrophorum. Nineteen of the strains were isolated from the colons of patients with chronic ulcerative colitis. According to the literature, some of these strains should be named Bacterium funduliforme and others Bact. necrophorum. Twelve strains isolated from bovine hepatic abscesses would qualify as representatives of the latter group.

The authors' purpose in this investigation was to compare the two groups in order to determine whether they were dealing with one or with two species of bacteria. Accordingly a study was made of the growth requirements of the strains, their colony structure, cell forms on different mediums, biochemical reactions, pathogenicity for rabbits and ability to cause ulceration of the colon in animals. In this study no sharp line differentiating these bacteria was found. There were morphologic variations of strain, but these were not sufficient for species differentiation. Likewise there was a difference in pathogenicity; only the 12 strains isolated from bovine hepatic abscesses were lethal to rabbits when injected subcutaneously. However, there were marked variations among the other strains in regard to their ability to produce lesions. The lesions produced with all

strains appear to be similar, but there seems to be a gradient from slightly virulent up to highly virulent, as represented by those strains isolated from bovine hepatic abscesses.

Bact. funduliforme and Bact. necrophorum are both associated with necrosis of the mucous membranes, and they give rise to metastatic abscesses in man and animals. Since there is no clearcut method for separating these two species, it appears better to retain the name, Bact. necrophorum. TOOMEY, Cleveland.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS. A. BROWN, Nebraska M. J. **23**:128 (April) 1938.

In a review of 41 cases in which operation was done successfully for congenital hypertrophic pyloric stenosis, attention is called to the fundamental points in diagnosis and the indications for selecting the time of operation. There were 33 males and 8 females. The average age at onset was a little over 21 days. In 4 cases in this series the symptoms began at birth. The latest onset was 42 days after birth. Vomiting was the most important symptom. A peristaltic wave was observed in all but 2 cases. A tumor was definitely palpable in 18 cases. Dehydration and loss of weight were present in all. The use of roentgen rays in diagnosis was not found necessary. Of postoperative measures, the most important is the restoration of water balance by hypodermoclysis, intravenous injection of fluids, blood transfusion or intraperitoneal injection of a salt solution. Of these methods, the last has been the method of choice in all of these cases. General anesthesia is preferred to local. Following local anesthesia, which was used in a few of these cases, Brown noted postoperative symptoms which did not seem to be those of postoperative shock but did correspond to symptoms of novocain (procaine hydrochloride) poisoning. On calculating the dose of novocain, it was found that with the use of only 10 cc. of 1 per cent novocain to anesthetize the abdominal wall in a baby weighing 5 pounds (2,268 Gm.), a lethal dose of the drug would be given if it were injected intravenously. The safety factor consists in the slow rate of absorption when the drug is given by the subcutaneous route. The possibility of an overdose of novocain is stressed.

HAMILTON, Omaha.

THE ACUTE ABDOMEN IN CHILDREN—APPENDICITIS. H. B. HAMILTON, Nebraska M. J. **23**:165 (May) 1938.

The mortality from appendicitis has not decreased but has increased in the last thirty-five years. Two thirds of the mortality occurs below the age of 12 and above the age of 40. The difficulty of diagnosing the condition in the child contributes to the high mortality at that age. The order of onset of the symptoms in childhood, viz., pain, nausea and vomiting, tenderness and fever, is the same as in the adult. To elicit the order of onset of the symptoms in the child requires careful questioning into the history and more careful examination of the patient.

Of 99 patients admitted to the University of Nebraska Hospital with the diagnosis of appendicitis, 81 were operated on for appendicitis. At operation 76 of these patients were found to have appendicitis. In the 18 patients not operated on infection of the upper part of the respiratory tract was the most common condition found. Of the 76 patients operated on whose diagnosis was confirmed, 56 had typical clinical findings in the following order: pain, nausea and vomiting, tenderness and fever.

FROM THE AUTHOR'S SUMMARY (HAMILTON, Omaha.)

CONGENITAL STEATORRHOEA DUE TO PANCREATIC DEFECT. M. H. HARPER, Arch. Dis. Childhood **13**:45 (March) 1938.

Eight cases of this condition are reported, with detailed clinical and laboratory data. In 4 cases the results of postmortem examination are given. Common to

all these cases was a failure to thrive on a normal diet. Also, the character of the stools was the same in all, i. e., they were bulky, offensive and a pale cream or pale green. They contained large amounts of unsplit fats.

KELLY, Milwaukee.

PNEUMOCOCCIC PERITONITIS. R. C. NEGRO, Arch. de pediat. d. Uruguay **9**:156 (March) 1938.

Negro presents the case of a 9 year old girl with the diagnosis of typhoid. During the thirteenth day of her convalescence ascites developed. Drainage of the abdomen was followed by complete cure.

SCHLUTZ, Chicago.

GASTROINTESTINAL HEMORRHAGE IN TOXIC STATES OF INFANTS. E. PELUFFO, Arch. de pediat. d. Uruguay **9**:171 (March) 1938.

Peluffo reports 2 cases of severe gastrointestinal hemorrhage occurring during severe infection, with toxemia, in infants. The patients were 8 months and 4 months old, respectively. At autopsy no macroscopic lesions were found in the intestines to explain the hemorrhages. It is believed that vasomotor and other nervous factors were possibly the cause of the hemorrhages.

SCHLUTZ, Chicago.

STRIATIONS ON THE MUCOUS MEMBRANE OF THE CHEEKS. G. O. HARNAPP, Monatschr. f. Kinderh. **73**:153 (May) 1938.

The writer calls attention to certain fine striations, somewhat variable, which appear on the mucous membrane of the cheeks of infants. He has attempted to determine the factors influencing them. He concludes that they are largely on a constitutional basis; they are affected by the weather and also by incidental nasal infections and grip.

GERSTLEY, Chicago.

CLINICAL MANIFESTATIONS OF AN INTRAMESENTERIC DIVERTICULUM OF THE SMALL INTESTINE. A. NORMARK, Acta pædiat. **20**:475, 1938.

Whereas Meckel's diverticulum is a common appendage of the small intestine, the intramesenteric diverticulum is extremely rare: Meckel's type is said to be encountered in from 1 to 4 per cent of autopsies, while only 16 examples of the intramesenteric variety have been referred to in print. Meckel's diverticulum is indisputably the result of incomplete involution of the fetal omphalomesenteric duct; the genesis of the type described in this paper is uncertain. It is substantially a reduplication of the intestine, lying parallel with it, between the leaves of the mesentery, and varying in length from 10 to 50 cm.; the lumen communicates with that of the intestine proper by a single opening of varying degrees of patency. Like other types of congenital diverticulum, the intramesenteric may contain patches of ectopic alimentary mucosa, which are sometimes the site of ulceration and bleeding.

Of the 16 previously reported cases, the greatest number were published in the American literature. In only a single instance did the lesion fail to produce symptoms. The outstanding elements of the clinical picture are bouts of melena with bright red or tarry stools and episodes of paroxysmal abdominal pain that usually occur in close chronologic relationship to the intestinal bleeding. Vomiting, diarrhea and the presence of a palpable abdominal mass are common but variable features. Obviously, the foregoing manifestations do not serve to distinguish the intramesenteric from Meckel's diverticulum or from intestinal polyps, ulcers and other causes of like phenomena. In 4 of the previously reported cases and also in the present case a finding was encountered that was so singular as to constitute a diagnostic point of considerable importance, namely,

the presence of one or more intrathoracic cysts. Available evidence indicates that these are retention cysts lined by intestinal epithelium. The intramesenteric diverticulum may produce symptoms in early infancy or may fail to yield signs until late childhood; it is probable that some are entirely asymptomatic. The treatment is surgical. Inasmuch as their removal presents a difficult technical problem, the operative mortality is high. The article includes a bibliography.

McCUNE, New York.

GLYCOGENESIS. F. KARLSTRÖM, Acta pædiat. **20**:497, 1938.

A recent review of the literature reveals that reports of 33 cases of von Gierke's disease, otherwise known as glycogen storage disease, have been published. In 5 or 6 of these cases autopsy was performed. Twenty of the patients were boys. Thirteen were girls. Ordinarily the disease does not present hereditary or familial characteristics; in a few instances, however, siblings were affected. The outstanding clinical feature of von Gierke's disease is enormous enlargement of the liver, unassociated with evidence of portal obstruction. In many cases the patient's head and trunk appear disproportionately large in comparison with the extremities; nutrition is apt to be impaired, and general physical development is usually considerably delayed; mental development is not affected. Moderate anemia is the rule. The serum calcium, the serum inorganic phosphorus and the serum chloride remain within normal limits; the glycogen of the blood is apt to be increased; the serum cholesterol has been found elevated in a few cases. The basal metabolic rate has been rather high in 2 or 3 instances. A characteristic feature of the disease is the consistently low level of the blood sugar during fasting; the concentration is apt to be between 40 and 60 mg. in 100 cc. The dextrose tolerance curve is similar to that obtained in cases of severe diabetes. Parenteral administration of epinephrine either fails entirely to produce an increase of the blood sugar or causes a less marked rise than that which occurs in healthy persons. The fall of blood sugar following injection of insulin is so marked as to be dangerous. Ketosis occurs quickly following brief periods of starvation. The prognosis for the disease is indeterminate: Several of the patients have survived to early adult life. The morbid anatomy of the disease consists principally in deposits of glycogen in the liver, muscular system and kidneys. The genesis of von Gierke's disease is uncertain; inability of the body to mobilize glycogen appears to be an important feature.

Karlström reports the case of a 1 year old boy who presented the characteristic manifestations of glycogen storage disease. The dextrose tolerance test and the response to epinephrine were typical. Puncture of the liver yielded a small amount of material, which when submitted to histologic examination revealed a large amount of glycogen within the liver cells. The diagnosis was confirmed at autopsy. Chemical examination of the liver, heart, skeletal muscle, kidney and brain showed increase of the glycogen of these tissues. Puncture of the liver is recommended as a worth while diagnostic procedure. The differentiation of von Gierke's disease from other types of chronic enlargement of the liver may be exceedingly difficult. A bibliography is supplied.

McCUNE, New York.

## Nervous Diseases

RESULTS OF FIFTEEN YEARS' EXPERIENCE WITH THE KETOGENIC DIET IN THE TREATMENT OF EPILEPSY IN CHILDREN. H. F. HELMHOLZ and M. GOLDSTEIN, Am. J. Psychiat. **94**:1205 (March) 1938.

In this report the authors attempt to answer two questions: 1. Previous reports have estimated that 50 per cent of the patients who have idiopathic epilepsy can be benefited by the ketogenic diet, 30 per cent being rendered free from attacks and 20 per cent becoming improved. Do these studies of fifteen

years, with 409 patients, bear out these earlier estimates? 2. If a patient who had idiopathic epilepsy has become free from attacks following the use of the ketogenic diet, what are the possibilities that this patient will have a recurrence of seizures?

Statistical analysis of these cases, according to the authors, warrants the following conclusions: The recurrence of seizures among patients who have become free from attacks ranges from 5 to 10 per cent over a period of seven years following the last attack. If a patient has gone for seven years without a seizure the possibility of a return of convulsions is slight.

JAHR, Omaha.

INFLUENZAL MENINGITIS. R. H. YOUNG and C. MOORE, Arch. Pediat. **55**:282 (May) 1938.

A patient with influenzal meningitis recovered under treatment with serum and sulfanilamide. The case is reported and the therapy described.

ORR, Buffalo.

TUBERCULOUS MENINGITIS RESEMBLING DIABETIC COMA. L. L. KRAFCHIK and L. B. SLOBODY, Arch. Pediat. **55**:288 (May) 1938.

A case is reported.

ORR, Buffalo.

FUNCTIONAL SPASMS IN CHILDREN. J. EPSTEIN, Arch. Pediat. **55**:301 (May) 1938.

The subject is discussed, with considerable generalization as to treatment.

ORR, Buffalo.

FOLLOW-UP STUDIES OF THE 1933 ST. LOUIS EPIDEMIC OF ENCEPHALITIS. J. F. BREDECK, G. O. BROWN, T. C. HEMPELMANN, J. F. MCFADDEN and H. D. SPECTOR, J. A. M. A. **111**:15 (July 2) 1938.

A follow-up study was made of the patients who suffered an attack of encephalitis in the 1933 epidemic in St. Louis. Sixty-six per cent showed complete recovery. Only 6.3 per cent are physically unable to resume their previous occupations—a comparatively low percentage. Parkinsonism is as yet rare. Mild nervousness, headache and other neurologic complaints are the commonest sequelae.

HEERSMA, Kalamazoo, Mich.

A STUDY OF PORENCEPHALY. A. LAIRD, J. Nerv. & Ment. Dis. **87**:317 (March) 1938.

Porencephaly is classified as plasmic and somatic. Under plasmic Laird places the inherited defect, in which the gene, alone or in combination, accounts for defective development of the brain, and blastophthoria, in which a healthy germ plasm is altered by toxic influences before fertilization. The somatic type includes porencephaly due to congenital, natal and acquired influences. These factors are considered individually.

A case is reported in which the patient, a girl, had been observed continuously from the age of 5 years until her death, at the age of 15 years. She had complete paralysis of all extremities and no control of bowel or bladder. Her weight had never exceeded 40 pounds (18 Kg.). She was never able to sit up and manifested no reaction to pain by crying or by attempted movement of the extremities. Her mental age was less than a year. No convulsive seizures were ever observed. She was born in 1915 at full term, with delivery normal. Both parents and an older sister were mentally deficient. A paternal uncle was insane.

At necropsy the brain weighed 650 Gm. The dura was greatly thickened, and there was bulging in both the parietal regions. The middle meningeal artery

was enlarged and stood out prominently on each side. The covering of the cortical defects, while attached to the rim of the cortex, was also joined to the arachnoid covering of the rest of the brain. The cortical defect on the left side measured 4 by 6.5 cm., and the entire length of the left cerebral hemisphere was 11.5 cm. Almost the entire cortical covering of the left lateral ventricle was absent. The defect on the right hemisphere was located slightly anterior to the defect on the opposite side, including more of the frontal than of the parietal lobe. The defect of the right hemisphere measured 3 by 5 cm. The entire cortex presented a simple convolutional pattern with microgyri and an asymmetry of the hemispheres.

JAHR, Omaha.

EPILEPSY: A PAROXYSMAL CEREBRAL DYSRHYTHMIA. F. A. GIBBS, E. L. GIBBS and W. G. LENNOX, Brain **60**:377, 1937.

Knowledge obtained by the use of the electroencephalograph in cases of epilepsy has given a clearer understanding of the pathophysiologic process underlying this condition. It is now known that epilepsy is associated with changes in the rhythms of the cerebral cortex; it is a "paroxysmal cerebral dysrhythmia." This discovery places the study and understanding of epilepsy on a different and deeper level and requires reorientation of thinking. In the past few years the authors have made electroencephalographic records of about 400 epileptic patients. As a result of this and previous studies they record seven new facts: 1. Seizures involving the cortex are accompanied by distinct characteristic fluctuations in the action potentials of the brain. However, several patients who had seizures while under observation showed no abnormality of recorded cortical rhythm during these seizures. The authors believe that in these patients the disturbance in rhythm involved a portion of the brain other than those for which potentials were being recorded. While it is possible to record the activity of six cortical areas simultaneously, all parts of the cortex are not accessible from the surface of the head, and, more important, disturbances confined to subcortical areas are not recorded. The few seizures which were not accompanied by abnormal cortical rhythms were bizarre in pattern, falling in the group of "epileptic variants." If a patient has a tonic-clonic convulsion during which he shows no abnormalities of cortical activity, he may be either hysterical or malingering, for in grand mal the disturbance involves the entire cortex and is therefore readily detected with electrodes on any part of the head. The absence of electrical abnormalities does not permit a differential diagnosis of hysteria or of one of the bizarre forms of epilepsy. The presence of abnormalities in the electroencephalogram may, however, demonstrate that in certain cases unexplained muscular jerkings, temper tantrums or moments of abstraction are really minute petit mal or psychomotor seizures. 2. The three main types of seizure have distinctive rhythms: The grand mal attack has a fast rhythm, the psychomotor attack a slow rhythm, and the petit mal episode an alternating fast and slow rhythm. The exact pattern of the seizure tends to be characteristic for each patient. 3. Antecedent to these gross abnormalities of rhythm is a lack of competent control of cerebral rhythms. Conditions such as excitement, closing the eyes or sleep, which modify the rate of the normal cortical rhythm, place a strain on the rate-regulating mechanism of the epileptic person which it frequently is unable to meet. The authors believe this accounts for the tendency of seizures to occur on waking or on falling asleep. Seizures that follow emotional upsets, which cause moderate changes of rhythm even in normal persons, are often called psychogenic. In general, electroencephalograms made from time to time in the case of an epileptic person show more variations than repeated electroencephalograms in the case of a normal person. 4. Some patients have subclinical seizures, which are typical short disturbances of rhythm not attended by subjective or objective evidence of a seizure. Subclinical petit mal attacks are more frequent than grand mal. They are seen usually in the records of patients with a history of very frequent petit mal attacks. How-

ever, recorded petit mal lasting for five, ten or fifteen seconds may be unaccompanied by clinical manifestations and may be taken from patients without a history of petit mal. 5. There is evidence that grand mal may be predicted many hours in advance. 6. In some patients abnormal activity begins in one area of the cortex and spreads to involve other areas. In a number of patients the abnormal waves of subclinical seizures were entirely confined to a specific area. One such patient was greatly improved after bilateral amputation of the frontal lobes. 7. Electroencephalography has been found useful in determining the value of various methods of therapy without the necessity of waiting for clinical seizures. Because anticonvulsant drugs slow cortical rhythms, they are more effective in grand mal than in other types of seizures. The inhalation of carbon dioxide and the administration of dextrose abolish certain abnormal rhythms temporarily. In some patients attention prevents the development of abnormal rhythms.

SALL, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

A BOY EXHIBITING NERVOUS SYMPTOMS ASCRIBED TO KERNICTERUS WITH SEPTIC NEONATAL JAUNDICE AS CAUSE. R. LIGHTWOOD and T. COLVER, Proc. Roy. Soc. Med. **31**:559 (April) 1938.

A boy 2¾ years old, the first child of his parents, was brought to the hospital because he was unable to speak or walk. On the fourth day of life the umbilicus became inflamed, and on the next day a purulent discharge was noticed, which lasted until the eighteenth day. On the eighth day jaundice appeared and was present for twelve weeks. During this period there were two convulsions, each lasting a few minutes. The progress of the child after the disappearance of jaundice seemed satisfactory. However, he did not sit up until the age of 10 months. The parents felt that he was quite intelligent. On examination his movements were found to be unsteady and clumsy, and there were involuntary movements of the head, trunk and limbs. Coarse nystagmus was present. The Wassermann reaction of the patient's and of the mother's blood was negative. Muscle electric reactions showed no gross abnormality. The authors in their comment state that the only reason for suggesting that the symptoms were due to kernicterus is that there was a clear history of prolonged neonatal jaundice of septic origin.

WILLIAMSON, New Orleans.

SUGAR IN THE CEREBROSPINAL FLUID. H. WARENBOURG, Gaz. d. hôp. **111**:317 (March 9) 1938.

Warenbourg states that the sugar in the cerebrospinal fluid is lower than the sugar in the blood, shows greater variations and varies whether ventricular fluid or spinal fluid is examined.

In purulent and tuberculous meningitis the sugar in cerebrospinal fluid is definitely decreased, while it is likely that the high values in encephalitis are related to higher level of sugar in the blood. Phlorhizin lowers the sugar in the cerebrospinal fluid; epinephrine increases it.

KAJDI, Baltimore.

ELEVATED NONPROTEIN NITROGEN IN MENINGEAL HEMORRHAGE. L. RIMBAUD, H. SERRE and J. BOUCOMONT, Gaz. d. hôp. **111**:965 (July 27) 1938.

Of 13 cases of meningeal hemorrhage in which the nonprotein nitrogen of the blood was determined, it was found elevated in 9 (from 58 to 130 mg.). In 4 of these cases there was a history of renal disease. The elevation was noted immediately; it reached the peak in about forty-eight hours and disappeared in from three to ten days. It was not accompanied by any sign of uremia and probably was due to absorption of the extravasated blood. Such a rise need not be regarded as a bad prognostic sign, as all the 5 patients recovered.

The authors warn one not to interpret a high level of nonprotein nitrogen as evidence pointing necessarily to uremia.

KAJDI, Baltimore.

A Case of von Economo's Encephalitis. A. Veritti, Lattante **9**:171 (April) 1938.

In a 4 year old boy a febrile illness developed, with convulsions, early in September, a few weeks after an attack of diarrhea. As sequelae, he showed left-sided spasticity, choreiform movements and tremor. During the acute stage the spinal fluid was under increased pressure. It contained 6 cells, and the Pandy test was positive. An analysis for sugar showed that it was present in a concentration of 0.11 per cent.

Higgins, Boston.

Electrocardiographic Findings in Spasmophilia. O. Cammann, Monatschr. f. Kinderh. **73**:42 (April) 1938.

Cammann reports 4 cases of spasmophilia in which changes were observed in the electrocardiogram: prolongation of the QT complex, with changes in the T wave, the latter showing a higher, sharper angle.

Gerstley, Chicago.

Tryptophan Reaction of Cerebrospinal Fluid. C. Sato mi, Acta pædiat. japon. **44**:198 (Feb.) 1938.

In 69 tests performed on cerebrospinal fluid obtained in 54 cases of tuberculous meningitis the tryptophan reaction was positive with the dilution of 1:100,000 in all cases. The dilution which gives a positive reaction in normal fluid is 1:150. In a very limited number of diseases of the central nervous system other than tuberculous meningitis this reaction is positive, but the universal positive reaction in cases of tuberculous meningitis indicates the tryptophan test to be one of the reliable methods for diagnosis of this disease.

Kato, Chicago.

A Nosocomial Epidemic of Acute Lymphocytic Meningitis of the Subclinical Type in a Service Restricted to the Treatment of Children with Pertussis. J. H. Magnuson, Acta pædiat. **20**:265, 1938.

The occurrence of whooping cough in a large number of children in Stockholm, Sweden, during the fall of 1936 required the opening in the hospital for epidemic diseases of a special ward for children suffering from this disease. In each of 20 children who were admitted to this service during the period of forty-three days between Dec. 9, 1936, and Jan. 20, 1937, lumbar puncture was performed. This routine measure brought to light quite fortuitously the occurrence of an epidemic inflammatory disease of the central nervous system, which was first thought to be etiologically related to whooping cough but which was subsequently judged to be an independent entity. Of the 20 children, 7 were affected. The disease began abruptly with an extreme paucity of clinical symptoms: Uniformly the children manifested a sudden rise of temperature to 39 C. (102.2 F.) and mild, poorly localized headache. Examination failed to reveal evidence of pathologic changes in the central nervous system or, for that matter, evidence of meningeal irritation. The spinal fluid was limpid, and the pressure was not elevated. A slight increase of protein was observed consistently. The concentration of sugar was normal, both absolutely and in comparison with the blood sugar. A moderate increase in the cell count was present at the time of onset of the disease; the average concentration amounted to about 100 cells per cubic millimeter; in 2 cases more than 200 cells were present. Nearly 100 per cent of the cells were mononuclear. The fever lasted a day or two; the headache, from a few hours to an entire day. The pathologic alterations of the spinal fluid persisted for as long as ten days after the onset of the illness. No untoward sequelae were observed in those patients who were examined three months after recovery. The etiologic nature of the infection was not uncovered. Tuberculosis and syphilis could be excluded without difficulty; poliomyelitis appeared unlikely but could not be ruled out. The results of the author's own

researches into the composition of the spinal fluid during pertussis, taken in conjunction with the most recent observations of other investigators of this matter, made it seem improbable that the phenomenon was the result of infection with the Bordet-Gengou bacillus. The disease is tentatively classified in the category of acute lymphocytic meningitis of the type that has been described by Wallgren in Sweden, by Armstrong and Lillie, by Traub, Rivers and Scott and by others in America, and by Lépine and Sautter in France. The bibliography is useful.

McCune, New York.

## Psychology and Psychiatry

Psychoanalytic Remarks on Alice in Wonderland and Lewis Carroll. P. Schilder, J. Nerv. & Ment. Dis. **87**:159 (Feb.) 1938.

Schilder submits an interesting psychoanalysis of Lewis Carroll (Charles Lutwidge Dodgson), the author of "Alice in Wonderland" and "Through the Looking Glass." The psychologic effect of these stories on the child who reads them is considered.

Jahr, Omaha.

Disabilities in Speaking and Reading. E. M. Cole, M. Clin. North America **22**:607 (May) 1938.

Language is a system of symbolic representations. As such, like any code, it must be learned in order to be of use. The ability to acquire skill in the art of speech varies with the human being. With some, hereditary endowment makes possible the acquirement of a facility which others never attain. Three types of speech disability frequently noted are: (1) motor delay of speech in otherwise neurologically sound children, (2) "baby talk" and (3) stuttering.

Another type of language difficulty encountered in school is the inability to read or spell. In this type heredity is no doubt an important factor, for a study of the family history usually discloses such significant features as stuttering, delayed speech, "baby talk" and left handedness.

The significance of left handedness in the heredity of children with speech disturbances is discussed at some length by Cole. The areas of the brain presiding over speech and over the understanding of speech, reading and writing are located in one hemisphere only, usually the left, the "dominant hemisphere." In this hemisphere is also usually located the center for the most skilled hand. Phylogenetically, skill in language is very young and consequently insecure. The possibility then exists that in fusing two inheritances which are antagonistic as far as cerebral dominance is concerned, i. e., left-handedness and speech, the perfect functioning requisite for the latter may be impaired.

In the treatment of these disabilities an effort should be made, by careful planning and drill, to strengthen the dominant hemisphere. This, in the case of language, is accomplished by reenforcing the deficient skill with a well performed skill, such as reading aloud and writing. In none of these various disabilities is anything accomplished by sporadic attempts at correction; only by repeated drilling can the necessary skill be acquired.

Eugene H. Smith, Ogden, Utah.

Mental Hygiene Aspects of Pediatrics. J. W. Bruce, South. M. J. **31**:910 (Aug.) 1938.

Bruce discusses various aspects of the child from the point of view of mental hygiene and particularly anorexia of psychic origin. Regarding the latter condition he suggests the following line of treatment: 1. Allow no distractions to occur when the child is eating. 2. Do not coax the child to eat. Do not threaten the child with punishment. 3. Set a time limit of from twenty to thirty minutes for the meal.

Schlutz, Chicago.

II. Beginnings of Human Personality. M. Acqua, Méd. inf. **9**:140 (May) 1938.

This article is the second dealing with psychologic observations on children from birth to 6 years of age. The present chapter deals with the development of conceptions of time and space.

Higgins, Boston.

Clinical, Etiologic and Therapeutic Study of Mongolism. Lereboullet, Nourrisson **26**:133 (May); 197 (July) 1938.

This is a careful study of mongolian idiocy, based on a large experience. The physical and the peculiar mental states are ably analyzed and described in detail. The author stresses the observation that patients with mongolian idiocy very often are musical but only in a very primitive way, owing to the low grade of intelligence. They listen and react to music but, for instance, are never able to sing. Without treatment they seldom surpass the mental age of from 2 to 3 years. With treatment, however, the author believes he has helped them reach a mental age of from 6 to 8 years. Though some similarity to states of hypothyroidism is admitted, identification of the two diseases is denied. The author reports an interesting observation of two brothers, one of whom was definitely suffering from hypothyroidism and the other of whom was a mongolian idiot. The mongolian spot has nothing to do with the disease in question and is found even very rarely in mongolian idiots. It is generally assumed that 75 per cent of these children die before puberty and from 95 to 100 per cent before reaching the age of 25 years. The author believes that these figures are somewhat exaggerated. The typical facies of mongolian idiocy seemed very much less outspoken in the few adult mongolian idiots observed, so that recognition of this disease in them might be more difficult than in children. Their intelligence never was sufficiently developed to allow them to work regularly. Fifty per cent of the deaths in mongolian idiots are due to pneumonia; 20 per cent, to congenital heart malformations. The author himself had not obtained consent for a postmortem examination of any of his own patients but mentions L. Babonneix (*Arch. de méd. d. enf.* **12**:497 [July] 1909), who described what he believed were typical changes in the brain. Etiologically the author emphasizes that (1) very rarely more than a single child in one family is a mongolian idiot, (2) the age of the mother seems to be of greater importance than the age of the father, (3) repeated pregnancies aid the production of mongolism, (4) states of exhaustion (world war experience) of conception are at times of importance, and (5) syphilis plays a role at times. The condition certainly is not hereditary. As far as treatment is concerned, the author advises administration of calcium, phosphates, iodine, iron, vitamins and extracts of the thyroid and thymus glands and liberal use of phenobarbital. Treatment by a highly trained child psychiatrist is strongly advocated, since it can considerably improve the usually desolate mental state of these children.

Heymann, Cleveland.

A Test for the Study of Childhood Fantasy. W. Stern, Ztschr. f. Kinderpsychiat. **5**:5 (May) 1938.

For the past several years Stern has utilized pictures or paintings depicting clouds as a means of obtaining the reactions of children. The test is carried out in a way similar to the Rorscharch blot test. The subject is allowed to supply his own interpretation of these pictures, relating his thoughts on what he sees to the examiner.

Jahr, Omaha.

Causes and Significance of Nocturnal Grinding of the Teeth. R. Goldmann, Acta pædiat. **20**:370, 1938.

Although grinding of the teeth during sleep may be more common in children of neuropathic constitution, its basic cause is not emotional instability but catarrhal

inflammation of the upper respiratory passages. Fundamentally, it is a reflex phenomenon that is related to chewing; the reflex can be liberated by the mucous secretions that accumulate in the presence of chronic nasal obstruction. In cases in which removal of the tonsils and adenoids does not relieve the symptom, careful local treatment of the nasal passages and paranasal accessory sinuses may bring about the desired result. Illustrative cases are recounted.

McCune, New York.

## Diseases of the Genitourinary Tract

Effect of Male Hormone upon the Descent of the Testes. J. B. Hamilton, Anat. Rec. **70**:533 (April 25) 1938.

Macacus rhesus is naturally cryptorchid up to the age of 3 to 5 years. Twelve monkeys were given injections of testosterone acetate or testosterone propionate; six monkeys were used as controls. Following this treatment, in each monkey the testes descended into the scrotum, and edema and swelling were less than when a gonadotropic substance was administered. It is suggested that the gonadotropic substance obtained from the urine of pregnant women may act by stimulation of the production of androgen.

Snelling, Toronto, Canada.

The Treatment of Renal Rickets. G. Graham, Arch. Dis. Childhood **13**:1 (March) 1938.

Two patients with renal rickets have been treated with sufficient alkali to restore the alkali reserve to within normal limits and at the same time with large doses of vitamins D and A (6,000 units of vitamin D and 30,000 units of vitamin A daily). The general condition improved; they grew in height and gained weight; the state of the kidney was slightly improved; the anemia was little altered, while the condition of the bones was greatly improved.

Kelly, Milwaukee.

A Foreign Body in the Kidney. N. B. Capon, Arch. Dis. Childhood **13**:85 (March) 1938.

Capon reports a case in which a hair slide was found in the right kidney. A part of the hair slide still extended through the posterior wall of the duodenum. The patient had swallowed the hair slide about one year before the operation on the kidney.

Kelly, Milwaukee.

Porphyrinuria Following Sulphanilamide. C. Rimington and A. W. Hemmings, Lancet **1**:770 (April 2) 1938.

An abnormally high level of porphyrin was found in the urine of nearly every patient treated with sulfanilamide.

Sulfanilamide was also administered to normal healthy white rats, in their diet, and marked increases in urinary and fecal porphyrin resulted. Animals killed at the height of the sulfanilamide dosage exhibited only a slight degree of histologic abnormality in the liver and kidneys, but the spleens were blackish brown and showed extensive deposits of a greenish brown granular pigment, much stainable iron and a certain amount of porphyrin.

The evidence available suggests that a certain degree of destruction of blood cells is caused by sulfanilamide in the doses employed, but it is felt that the disturbance in pigment metabolism is not to be explained by this fact alone. A more deep-seated effect on the hemopoietic system is suspected, analogous possibly, in some ways, to the toxic action of lead.

Langmann, New York.

SEXUAL DEVELOPMENT OF THE CHILD AND ADOLESCENT. H. CRICHTON-MILLER, Practitioner **141**:243 (Sept.) 1938.

In an interesting concise outline the author enumerates "the steps by which the human subject gropes his way from simple instinctive hedonism to rational sex control in maturity. It cannot be claimed that his progress is easy, nor is his final achievement always worthy of high praise. But let it always be remembered that the man of today is still a transitional type, passing from simple instinctive motivation to rational control and idealistic purpose."

GELSTON, San Francisco.

ANOMALIES OF THE GENITOURINARY TRACT AND THEIR IMPORTANCE IN CHRONIC PYELITIS. G. CARDELLE, Bol. Soc. cubana de pediat. **10**:159 (April) 1938.

In all cases of acute pyelitis, particularly when the inflammation is severe and has not responded to any form of treatment, one is justified in suspecting that there is an anomaly of the urinary tract. Cystoscopic investigation and urethral catheterization are perfectly harmless in the hands of an expert cystoscopist and may be of great clinical use. There are less severe reactions following cystoscopic examination in children than in adults.

The author found that a complete urologic investigation was possible in every case of chronic pyelitis. He stresses the need of more cooperation between the pediatrician and the urologist and favors the use of roentgenograms.

SCHLUTZ, Chicago.

## Diseases of the Ductless Glands; Endocrinology

STUDIES OF THE ISLANDS OF LANGERHANS AFTER CONTINUOUS INTRAVENOUS INJECTION OF DEXTROSE. C. A. WOERNER, Anat. Rec. **71**:33 (May 25) 1938.

When a moderate increase in the blood sugar of the guinea pig is maintained by continuous intravenous injection of dextrose, a diabetic condition does not result. In many of the animals there is an intense compensatory increase of island tissue. This brings about an increase in the metabolic rate.

SNELLING, Toronto, Canada.

RATES OF GROWTH, OSSEOUS DEVELOPMENT, AND MENTAL DEVELOPMENT IN CRETINS AS A GUIDE TO THYROID TREATMENT. L. WILKINS, J. Pediat. **12**:429 (April) 1938.

This paper presents a method of following and comparing the rates of growth, osseous development and mental development in cretins. The method is of special help in following the results of therapy and regulating the dose of thyroid extract.

In this method the measurements are reduced to terms of "height age," "bone age" and "mental age" in the following manner: The actual height of the patient is compared with a standard anthropometric table which shows the age at which the "average" child of the same sex would attain this height and this is considered the patient's "height age." The "bone age" is determined by study of the various centers of ossification in roentgenograms of the joints and by comparison of the observations with tables showing the normal time of their appearance. The "mental age" is determined in infancy by the developmental schedules devised by Gesell and in older children by the Stanford revision of the Binet-Simon tests. The height age, bone age and mental age are each plotted in graphs on the same chart, with observations made from time to time while the patients are receiving thyroid medication. In the charts the patient's chronologic age is plotted along the abscissas and the developmental age along the ordinates. The normal rate of development is represented by a straight line rising at 45 degrees from the

horizontal. The relative position of the graph of height age, bone age and mental age in respect to the normal line indicates the deviation from normal of each of these developmental processes. The position of the graphs in relation to each other indicates which of the developmental processes is the more retarded.

The developmental charts of 6 cretins treated with thyroid are included in the report. These charts show that administration of adequate doses of thyroid always causes marked acceleration in the developmental rates. The bone development always progresses rapidly toward the normal level. The growth rate increases less rapidly but usually parallels or exceeds the normal rate, whereas the mental development in some instances continues to lag behind the normal rate. The developmental rates, especially the rate of osseous development, serve as a reliable guide to the adequacy of thyroid treatment over long periods, whereas the clinical condition of the patient and the basal metabolic rate or blood cholesterol may give a deceptive picture of the amount of improvement. Wilkins believes that it is probably necessary to produce a mild degree of hyperthyroidism in order to accelerate the developmental rates sufficiently to allow the retarded hypothyroid patient to regain his lost years and approach his normal age level.

RAUH, Cincinnati.

ADRENAL CORTICAL HORMONE (CORTIN) IN BLOOD AND URINE OF PATIENTS WITH CUSHING'S DISEASE. E. ANDERSON and W. HAYMAKER, Proc. Soc. Exper. Biol. & Med. **38**:610 (June) 1938.

Extracts were made of the blood of 3 patients with unmistakable Cushing's disease, also of the urine of 1 of these patients and of the urine of a fourth patient (a girl of 5 years with an adrenogenital syndrome). These extracts were dissolved in olive oil and injected subcutaneously into adrenalectomized rats. Definite increases in the survival periods of the adrenalectomized rats were noted, a finding which tends to support the hypothesis that the symptoms of Cushing's disease are due to hyperfunction of the adrenal cortex as suggested by McQuarrie, Johnson and Ziegler (*Endocrinology* **21**:762, 1937). Attempts at determining the potency of the blood and urine indicated that 1 cc. of blood contained an amount of the adrenal cortical hormone equivalent to slightly more than that of the hormone contained in 4 Gm. of fresh adrenal gland, and a twenty-four hour specimen of urine, an amount equivalent to that of the hormone in 400 Gm. of tissue.

HANSEN, Minneapolis.

A CASE OF DIABETES MELLITUS IN A YOUNG INFANT. J. DEVINE, Arch. Dis. Childhood **13**:189 (June) 1938.

A case of diabetes mellitus occurring in a child aged 25 days is described. Postmortem examination revealed marked hypoplasia of the islet tissue of the pancreas. From a review of the literature it appears that only 3 other unequivocal cases of neonatal diabetes have been reported.

KELLY, Milwaukee.

THE DIETETIC TREATMENT OF THE AVERAGE DIABETIC. D. M. DUNLOP and R. PYBUS, Edinburgh M. J. **45**:415 (June) 1938.

This is the twenty-fifth paper under the title "Clinical Recollections and Reflections." Dunlop and Pybus state that there is an exaggerated belief in the difficulties of treating adults for diabetes mellitus. They make no attempt to consider the handling of unusual types of diabetes, such as that of childhood, for they have special problems of their own. They suggest that carbohydrate is a stimulus to the formation of insulin and that if it is too rigorously controlled in a diabetic patient a further inhibition of an already poor supply may take place.

NEFF, Kansas City, Mo.

EFFECT OF EXERCISE AND CHANGE OF CLIMATE ON DIABETES IN CHILDHOOD. G. MOURIQUAND and J. SAVOYE, Arch. de méd. d. enf. **41**:286 (May) 1938.

Bouchardat, Rathery and others have shown the importance of moderate exercise in the open air in the management of diabetes in adults. The influence of these factors, however, in the amelioration of diabetes in juvenile patients has not been sufficiently stressed. The use of insulin places the young organism in a most advantageous position to profit by a change in climate and systematized play. The authors present several case reports to illustrate the striking improvement in young persons with diabetes who have been transferred to salubrious mountain or maritime districts. The association of muscular exercise with a changed regimen of life is immediately reflected by reduced glycosuria and consequent lowered demand for insulin. To say whether such benefits will be continuous requires further observation.

AMESSE, Denver.

DIABETIC CHILDREN ON FREE DIET. K. BOJLÉN, Acta pædiat. **20**:310, 1938.

Bojlén reiterates the thesis which is being defended by an increasing number of Scandinavian physicians, namely, that the unconditional relaxation of dietary restrictions constitutes the logical sequel of the progressive advances in the treatment of juvenile diabetes which have been made during the last fifteen years. The principle of the free diet is the postulate, "it is preferable to leave it to the child's organism itself to formulate its dietary requirements." As far as Queen Louise's Hospital for Children is concerned, the contemporary commitment to the free diet is the result of the gradual growth of a tendency which is discernible in the hospital records several years back and which had its origin in physiologic and in humanitarian considerations. At the present time 16 children with diabetes are being treated in this institution without restriction of diet. Of these, the majority have been observed for two years or longer. Treatment is outlined according to the most tolerant principles. That is to say, the child must look well, develop normally and feel happy; the urine must remain free from ketone bodies. No importance is attached to the quantity of sugar excreted in the urine or to the concentration of sugar in the blood. In 7 of the 16 children the results, according to the author, could not possibly have been better; in the others there is evidence to suggest that the comparatively unsatisfactory results are due to environmental circumstances. It is possible that newer preparations of insulin may produce better results. Controlled experience in 8 cases demonstrates that the children make the transition from the measured diet to the free diet readily and satisfactorily from a physiologic point of view. In most instances only two injections of insulin are required daily. The children are not so often or so severely ill. Coma and precoma have occurred only twice. The sugar in the blood and urine remains high. It is open to discussion whether or not hyperglycemia is really or potentially harmful. Development appears to proceed satisfactorily. The protocols of 14 cases are presented, and a comprehensive bibliography is appended.

MCCUNE, New York.

## Diseases of the Eye

STRABISMUS. F. B. FRALICK, J. Michigan M. Soc. **37**:226 (March) 1938.

Fralick says strabismus is one of the most frequent of the ophthalmic conditions seen by the physician and the least understood. The following factors are listed as productive of strabismus: hereditary influences, defective fusion, refractive errors, abnormal extraocular muscle valence and congenital or acquired paresis or paralysis of one or more exraocular muscles. The steps in treatment are outlined, and a conclusion given which every physician should read and ponder.

CAREY, Detroit.

OCULAR OR PSEUDOTORTICOLLIS. M. T. HORWITZ, New York State J. Med. **38**:184 (Feb. 1) 1938.

Ocular torticollis (pseudotorticollis) is a compensatory adjustment of the head to overcome vertical diplopia due to paralysis of the superior or inferior recti or of the oblique muscles. It is corrected by the production of a similar defect in the good eye. Horwitz reports a case. AIKMAN, Rochester, N. Y.

A CASE OF PRIMARY BILATERAL ANOPHTHALMIA (CLINICAL AND HISTOLOGIC REPORT). E. RECORDON and G. M. GRIFFITHS, Brit. J. Ophth. **22**:353 (June) 1938.

The developmental anomaly reported in this article was seen in a male child. Pregnancy and labor had been normal. There was no history of a developmental anomaly in the family of either parent, and there was no consanguinity. The child died of bronchopneumonia at the age of less than 3 months. A detailed anatomic description of the brain is given. Serial sections were made of the orbits. The sections of the left orbit were vertical and those of the right horizontal. In both orbits the six extrinsic muscles and their nerves were found embedded in fat. On the left side, four rectus muscles were attached by their anterior end to a minute nodule of fibrous tissue containing pigment granules, apparently lying free and not containing any recognizable cell structure. The pigment was brownish and did not give a reaction to the test for iron. The nodule did not contain any trace of retinal neuroepithelium or any type of cell other than the fibrous tissue. On the right side the muscles were not attached to any fibrous mass.

The author maintains that the case is one of bilateral primary anophthalmia in which there has been an absolute failure in the development of the optic vesicles and that it is distinct from those cases of "degenerative" or "consecutive" anophthalmia in which the vesicles appeared to have formed and subsequently to have atrophied.

The article is illustrated. ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

VISUAL DEFECTS IN 11,021 SCHOOL CHILDREN OF MILAN. M. PAGANI, Ann. di ottal. e clin. ocul. **65**:812 (Nov.) 1938.

Of a large number of school children examined, 12.5 per cent had visual defects. Hyperopia was found in 3,605, astigmatism in 2,868, myopia in 2,451, anisometropia in 803 and amblyopia in 659. Strabismus was seen in 909, which is approximately 0.10 per cent of the student body during the period of twelve years, or 8 per cent of the number with visual defects. GIFFORD, Chicago. [ARCH. OPHTH.]

FAMILIAL HYPERMETROPIA OF HIGH DEGREE: CONSIDERATION OF THE PATHOGENESIS OF AMETROPIA. G. CAVALLACCI, Arch. di ottal. **44**:178 (May-June) 1937.

Three siblings of consanguineous parents showed high degrees of hypermetropia. After careful consideration of his own cases and those described in the literature, Cavallacci concludes that an eye showing a high degree of hypermetropia does not present a true anomaly but manifests in exaggerated form the characteristics of the eye with the usual degree of hypermetropia. This makes the problem of etiology one and the same.

Examination of the cranial measurements in his cases and in the cases of the usual axial ametropia revealed that frequently there was an association between brachycephaly and hypermetropia and between dolichocephaly and myopia. Cavallacci feels that this is an expression of an embryonal condition common to both the head and the eye; i. e., the cephalic anlage possesses morphologic characteristics that are congenitally fixed and in later development are transmitted either to the head itself or to the optic vesicle.

These congenital morphologic factors are probably hereditary in accordance with the frequent hereditary and familial character of the various ametropias. In conclusion, Cavallacci expresses the opinion that the aspect of consanguinity strengthened the hereditary factor of hypermetropia which was present in the family, resulting in the exaggerated expression of hypermetropia observed in his cases.

Included in the article is a statistical table showing the refractive errors found at the Royal Eye Clinic of Pisa from 1916 to 1936 and demonstrating the rarity of the condition described in addition to the frequency of other ametropias.

GUIDA, Chicago. [ARCH. OPHTH.]

## Skin Diseases; Allergy

COMMON SKIN DISORDERS IN CHILDREN. C. B. TAUBER and G. E. CLARKE, Arch. Pediat. **55**:1 (Jan.) 1938.

The diagnosis and treatment of diaper rash, impetigo contagiosa, intertrigo and eczema are discussed.

ORR, Buffalo.

VASCULAR BIRTHMARKS — TREATMENT WITH SCLEROSING SOLUTION. H. W. KAESSLER, J. A. M. A. **110**:1644 (May 14) 1938.

The article gives a description of a technic for sclerosing vascular birth marks by injection. The method is intended to supplant some of the more expensive and technical procedures now in use.

HEERSMA, Kalamazoo, Mich.

A STATISTICAL EVALUATION OF THE LEUCOPENIC INDEX IN ALLERGY. M. LOVELESS, R. DORFMAN and L. DOWNING, J. Allergy **9**:321 (May) 1938.

The experiments were conducted on five different groups of persons, one of which consisted of insensitive persons, one of patients sensitive to pollen, and three of patients sensitive to food.

The technic was modified so as to minimize the effect on the leukocyte count of such factors as activity and fasting. The resultant figures were arrived at by mathematical calculations. They do not support the contention that leukocytosis is the normal response to ingestion or that postprandial leukopenia is an index to incompatibility of foods. In the pollen-sensitive groups the change in the leukocyte level was insignificant when symptoms were produced by giving an extract of ragweed subcutaneously.

HOYER, Cincinnati.

THE LEUCOPENIC INDEX. E. A. BROWN and G. P. WADSWORTH, J. Allergy **9**:345 (May) 1938.

This is a lengthy article in which details of technic are minutely discussed. The authors conclude that differences of small order occur between different observers, instruments, drops of blood and changes of position.

Variations of the same order of magnitude were found to be present when a comparison was made of subsamples taken simultaneously or successively from normal fasting subjects, from normal subjects preprandially and postprandially and from allergic patients preprandially and postprandially, following the ingestion of either compatible or incompatible foods.

No adequate proof was found for the occurrence of either normal postprandial leukocytosis or anaphylactic postprandial leukopenia.

The technic used previously in this work were shown to be questionable as regards accuracy. The conclusions drawn were mathematically untenable. The authors in their series of over 2,000 leukocyte counts found no physiologic, pathologic or mathematical justification for the use of the leukopenic index test.

They feel too that the true issue is not whether there is a rise or a fall in the cell count but whether the rise or the fall is first mathematically, second physiologically and third allergically significant. They feel, therefore, that although their work and the literature do not necessarily discredit the leukopenic index test the papers describing the test are unconvincing.

HOYER, Cincinnati.

RELATIVE VALUE OF THE DIAGNOSTIC PROCEDURES IN THE ALLERGIC CHILD. A. V. STOESSER and R. E. CUTTS, Minnesota Med. **21**:418 (June) 1938.

Stoesser and Cutts feel that cutaneous tests and trial or elimination diets play an important part in the diagnosis and treatment of allergic disorders in the child. In eczema the procedures of greatest value are the elimination diets and pressure-puncture tests; in allergic rhinitis, the intracutaneous tests; in hay fever, the pressure-puncture tests; in bronchial asthma, the pressure-puncture and intracutaneous tests, and in urticaria and gastrointestinal allergy, the elimination diets. Their observations in 300 cases indicate that the allergic child can be treated with a minimum of time and effort if attention is given to the fact that each allergic disease has a diagnostic procedure or procedures to which it best responds.

ANDERSON, Minneapolis.

ARTHUS' PHENOMENON FROM MOSQUITO BITES: REPORT OF A CASE WITH EXPERIMENTAL STUDIES. A. BROWN, T. H. D. GRIFFITTS, S. ERWIN and L. Y. DYRENFORTH, South. M. J. **31**:590 (June) 1938.

The authors report a case of cutaneous necrosis in a white girl caused by the bite of Aedes aegypti, a common household mosquito of the South. An attempt at desensitization was unsuccessful. The authors conclude that necrosis of the skin following a mosquito bite is localized anaphylaxis and that it is an allergic phenomenon. They believe that this case is the first of its kind to be reported.

SCHLUTZ, Chicago.

ACRODYNIA OF CHILDREN. R. DARDANI, Lattante **9**:203 (May) 1938.

A 4 year old boy had symptoms of acrodynia for two months. Then he was given daily 1 mg. of synthetic vitamin $B_1$ by mouth. Eight to ten days later his appetite had returned, he was willing to stand, the psychic symptoms were disappearing, and the sweating, lacrimation and salivation were less. After fourteen days he was walking and seemed well except for slight lacrimation and cold, moist hands and feet. After twenty-one days he was well.

HIGGINS, Boston.

EDEMA WITH HYPOPROTEINEMIA IN INFANTS. A. ARIZTIA, Arch. de pediat. d. Uruguay **9**:246 (April) 1938.

In 3 infants with mild infections edema developed. Biochemical studies showed lowering of protein, especially in the serum (by one third), and changes such as are seen in lipoid nephrosis. Improvement occurred after the use of a high albumin, low salt, low fluid intake and abundant vegetables and vitamins. The genesis of the condition was mainly attributed to changes in the liver.

SCHLUTZ, Chicago.

PERINEOGLUTEAL ERYTHEMA IN INFANTS. B. VIGNALE and C. GIANELLI, Arch. de pediat. d. Uruguay **9**:278 (May) 1938.

Vignale and Gianelli claim that the perineogluteal erythema of infants may be considered in a great number of cases as a form of seborrheic eczema and that its localization in the perineogluteal regions is due to local factors.

SCHLUTZ, Chicago.

THE ASTHENIC CONSTITUTION AND ITS IMPORTANCE IN THE FUTURE HEALTH OF CHILDREN FROM A CLINICAL POINT OF VIEW. B. SORIA, Bol. Soc. cubana de pediat. **10**:155 (April) 1938.

Soria states that children with asthenia are predisposed to pulmonary infections not only because of the anatomic effects but also because of the effect on the diaphragm and subsequent results. The different factors producing such deformity are explained, and attention is called to its early correction.

SCHLUTZ, Chicago.

## Surgery and Orthopedics

INJURIES ABOUT THE SHOULDER JOINT IN CHILDREN, EXCLUSIVE OF FRACTURES OF THE CLAVICLE. JOHN E. SULLIVAN, Ann. Surg. **107**:594 (April) 1938.

The most common injury about the shoulder joint, excluding fracture of the clavicle, in children admitted to the children's surgical service of the Bellevue Hospital was fracture of the upper end of the humerus. In most of the cases fracture of the humerus was unaccompanied by associated injuries.

Good anatomic restoration of the fragments, while desirable, is not essential, as nature remolds the bone.

BANTIN, Omaha.

TREATMENT OF INFECTED WOUNDS WITH UREA. L. F. MULDAVIN and J. M. HOLTZMANN, Lancet **1**:549 (March 5) 1938.

Muldavin and Holtzmann report the results of the treatment of infected wounds with urea in a series of 170 cases. The results were so encouraging that the adoption of this method of treatment as a routine in the casualty department of the Royal Free Hospital is under consideration.

The advantages of the treatment are: (1) It is cheap; (2) it produces no dermatitis; (3) it deodorizes foul-smelling wounds; (4) it dissolves necrotic material; (5) local circulatory conditions are improved; (6) it has no toxic effect; (7) it has been successful in cases in which other treatments have failed.

Its disadvantages are: (1) It sometimes causes pain; (2) it does not stimulate epithelization.

LANGMANN, New York.

INDICATIONS FOR SURGICAL OPERATION ON THE SYMPATHIC NERVOUS SYSTEM. W. F. SUERMONDT, Nederl. tijdschr. v. geneesk. **82**:3443 (July 9) 1938.

According to Suermondt, the justifications for surgical treatment of the sympathetic nervous system are: (*a*) to afford relief from pain (e. g., angina pectoris, visceral pains, arterial pains, causalgia); (*b*) to correct a defect in visceral function (e. g., megacolon); (*c*) to diminish spasticity of muscles. The article is a communication of the author's own results.

VAN CREVELD, Amsterdam, Netherlands.

## Teeth and Dentistry

STUDIES ON DENTAL CARIES: I. DENTAL STATUS AND DENTAL NEEDS OF ELEMENTARY SCHOOL CHILDREN. H. KLEIN, C. E. PALMER and J. W. KNUTSON, Pub. Health Rep. **53**:751 (May 13) 1938.

A study was made of the dental status and needs of 4,416 grade school children in Hagerstown, Md. The findings are of great interest to any one interested in dental problems. The article should be read in full, as it is not well abstracted. It was found that in these children there were 23,753 decayed, missing or filled teeth, or an average of 5½ carious tooth surfaces per child. The authors believe that adequate dental care can be given to such school children only if each child's teeth are examined and treated every year. If this is done, the defects do not pile up and are more easily handled.

SANFORD, Chicago.

STUDIES ON DENTAL CARIES: VII. SEX DIFFERENCES IN DENTAL CARIES EXPERIENCE OF ELEMENTARY SCHOOL CHILDREN. H. KLEIN, Pub. Health Rep. **53**:1685 (Sept. 23) 1938.

In an analysis of the data from dental examinations of 2,232 boys and 2,184 girls, it appears that the girls had a higher number of carious teeth than did the boys of the same chronologic age. This is explained by the fact that their teeth erupt earlier than the teeth of boys and are thus exposed longer to attack by caries.

SANFORD, Chicago.

GREEN TEETH FOLLOWING ICTERUS GRAVIS. R. W. B. ELLIS, Proc. Roy. Soc. Med. **31**:767 (May) 1938.

A boy of 2½ years was noticed to be jaundiced eight hours after birth. At seven days he was admitted to the hospital, still deeply jaundiced. He was drowsy, and the liver and spleen were both enlarged. The red blood cell count was 999,000, and the hemoglobin content was less than 15 per cent. The child was given two blood transfusions, and iron and ammonium citrates was administered in the dosage of 5 grains (0.3 Gm.) three times daily. There was rapid improvement. The child was discharged well at the age of 12 weeks and has remained well ever since. At 6 months the two upper central incisors erupted and were olive green. He had twenty teeth at the time of the report, all of which were partially green.

WILLIAMSON, New Orleans.

THE TEETH OF CHILDREN OF THE FIRST AND SECOND GRADE IN PRAGUE. J. POKORNY, Československ. stomatol. **36**:253 (April) 1936.

In a medical survey made during the school year of 1935-1936, 10,888 children of the first and second grades were checked for caries and dental hygiene. Of these, 7,777, or 71.5 per cent, were in need of dental care, and 3,111, or 28.5 per cent, did not require dental care.

STULIK, Chicago.

DENTAL CARIES IN THE WHITE RAT AS A SEQUEL OF DISTURBANCES OF THE ACID-BASE EQUILIBRIUM OF THE ORGANISM: THE ROLE OF VARIATIONS IN THE ACID-BASE BALANCE IN DETERMINING THE OCCURRENCE OF DENTAL CARIES; A PRELIMINARY REPORT. S. FORSHUFVUD, Acta pædiat. **20**:409, 1938.

It is well known that agreement has not yet been reached concerning the genesis of dental caries. Miller's hypothesis, which includes as a primary factor the chemical solution of the teeth by acid secretions of the mouth and as a secondary factor the destructive action of bacteria, has been largely replaced by the theory of dietary deficiency, which is based on the work of Boyd, Drain, Hanke, Hawkins, Mellanby, Lennox, Price, Schiötz and others.

The author previously enunciated a specific formulation of the deficiency theory; this he reasserts in the following words: Dental caries "is not due to the composition of the diet per se . . . so long as the diet is adequate to maintain life . . . but to frequent alterations of diet. . . . Excessively wide and frequent alterations of diet give rise to disturbances of metabolism that result in caries of the teeth; this cannot be prevented by any diet, no matter how rich in minerals, vitamins and other protective substances, if the essential substances, vitamins, minerals, proteins, carbohydrates, etc., are supplied irregularly and variably as regards amount and type. . . . The advantages of adaptation are forfeited. A completely regular and monotonous diet is the only guarantee of sound teeth."

Dental caries has been produced in the white rat by several means, viz., by a diet high in carbohydrate, by diets low in phosphorus and in vitamin D and also by large amounts of vitamin D. The teeth of the white rat are extremely

sensitive to changes of diet; hence, the significance of these experiments is obscured by the failure of the investigators to note whether the caries occurred as a transient phenomenon shortly after the animals were placed on the experimental diet or whether it progressed over a period of time coextensive with the ingestion of the prescribed diet.

In the experiments reported in the present article, prolonged administration of ammonium chloride failed to produce caries in white rats; that of sodium bicarbonate gave rise to insignificant and transient caries in a small number of animals. Alternate administration of ammonium chloride and sodium bicarbonate resulted in severe, progressive caries. The lesions are illustrated with photographs, and an extensive bibliography is supplied. McCUNE, New York.

## Miscellaneous

GRAVE SEQUELAE OF BLOOD TRANSFUSIONS: A CLINICAL STUDY OF THIRTEEN CASES OCCURRING IN THIRTY-FIVE HUNDRED BLOOD TRANSFUSIONS. E. L. DE GOWIN, Ann. Int. Med. **11**:1777 (April) 1938.

In a series of 3,500 cases of blood transfusion in which for the most part sodium citrate was used as the anticoagulant and the blood administered by gravity through small needles, 7 deaths occurred which were directly attributable to the transfusions. Of the persons who died, 5 presented renal insufficiency and 2 pulmonary edema. The former complication may be prevented by alkalinization of the urine prior to the transfusion. Experimentally this has been shown to prevent obstruction of the tubules by hemoglobin. Pulmonary edema may be obviated by careful avoidance of an embarrassment of the right side of the heart due to excessive amounts of transfused blood. The necessity for cross matching in addition to typing of bloods is stressed. READING, Galveston, Texas.

PASSAGE OF SULFANILAMIDE FROM MOTHER TO FETUS. H. M. LEE, R. C. ANDERSON and K. K. CHEN, Proc. Soc. Exper. Biol. & Med. **38**:366 (April) 1938.

Sulfanilamide given to pregnant rabbits was found in considerable concentration in the fetus, also in the amniotic fluid. The acetylated form was relatively lower in the fetal blood than in the maternal blood. HANSEN, Minneapolis.

INFLUENCE OF VITAMIN D IN EXPERIMENTAL LEAD POISONING. A. E. SOBEL, O. GAWRON and B. KRAMER, Proc. Soc. Exper. Biol. & Med. **38**:433 (April) 1938.

Addition of vitamin D to the diets of rats suffering from experimental lead poisoning causes an increase in the concentration of lead in the blood stream, as well as in the bones. HANSEN, Minneapolis.

INFLUENCE OF DIETARY CALCIUM AND PHOSPHORUS UPON ACTION OF VITAMIN D IN EXPERIMENTAL LEAD POISONING. A. E. SOBEL, I. B. WEXLER, D. D. PETROVSKY and B. KRAMER, Proc. Soc. Exper. Biol. & Med. **38**:435 (April) 1938.

In animals receiving a diet in which phosphorus was high and calcium low the lead in the blood stream was extremely low. This occurred in spite of the fact that the lead in the high calcium, low phosphorus diet was three times as much. Thus the beneficial effect of high phosphorus in the diet in experimental and chemical lead poisoning may be explained in terms of lowered lead in the concentration of blood. Slightly more lead was deposited in the bones of the rats fed the high phosphorus, low calcium diet. HANSEN, Minneapolis.

RELATIVE RISE IN TEMPERATURE OF TISSUES HEATED IN THE HIGH FREQUENCY FIELD. H. J. TAYLOR, Brit. J. Phys. Med. **1**:82 (March) 1938.

Experimental work is presented in an attempt to demonstrate the relative rise in temperature in the high frequency field of various tissues. It was found that at the wavelengths used (from 6 to 3.5 mm.) fat is always heated to a far higher temperature than other tissues. With decreasing wavelengths, however, the relative heating of fat and other tissues becomes less. HARTMAN, Cleveland.

THE ROLE OF CHROMOTHERAPY IN MODERN MEDICINE AND SURGERY. R. D. HOWAT, Brit. J. Phys. Med. **1**:86 (March) 1938.

Howat believes that red rays can be used to advantage in the treatment of furunculosis, psoriasis, eczema, pustular acne, pruritus and persistent anal fissures. Infra-red plus luminous rays (tungsten filament lamp) screened with a red filter is recommended. He states that chromotherapy has proved itself to be a useful adjuvant in the treatment of measles, scarlet fever, chickenpox and smallpox.

The psychic effects of general irradiations are discussed. The closer the patient approaches the heat rays, the more stimulative the response. Green rays induce a retardation of psychic processes. General violet ray treatment is still more depressant in action. Red rays are mentally stimulating and productive of excitement and, according to other workers, are even capable of inducing hallucinations and delirium. HARTMAN, Cleveland.

A BACTERIOLOGICAL AND CLINICAL STUDY OF THE PROFESSIONAL PERSONNEL OF MATERNITY HOSPITALS, WITH SPECIAL REFERENCE TO CARRIERS OF HAEMOLYTIC STREPTOCOCCI. L. M. BRYCE and P. TEWSLEY, M. J. Australia **1**:639 (April 9) 1938.

From a study of the literature on puerperal infection and from bacteriologic studies in this disease the authors conclude that the upper part of the respiratory tract of the patient or, more frequently, some person with whom the woman in childbirth comes in contact is the most probable source of infection with pathogenic hemolytic streptococci. Therefore reduction of the incidence of such infection depends on the prevention of transfer of organisms from the upper part of the respiratory tract of the contact or of the patient to the genital tract. Swabbing of the nose and throat at short intervals is recommended to determine whether one or the other is a carrier of hemolytic streptococci of group A. The cultures obtained are subjected to biochemical, bacteriophage and precipitin tests for identification.

It is interesting that of 115 normal persons, hemolytic streptococci of group A were present in 10 (8.7 per cent), 9 of whom were known to have contacts with streptococcic infection. Of 34 persons showing evidence of chronic or recent acute infection of the respiratory tract, 8 (23 per cent) showed hemolytic streptococci of group A. Two of the latter (25 per cent) were known to have contacts with such infection. The cultures most positive for streptococci were obtained from among the nurses on night duty.

The incidence of throat carriers of streptococci of group A among persons having contacts with 3 mothers suffering from puerperal infection was 22 per cent. The incidence of positive cultures among doctors and nurses who had no known contacts with streptococcic infections was 3 per cent and 6.7 per cent, respectively.

GONCE, Madison, Wis.

THE JAPANESE INFANT. G. A. PATEY, Arch. de méd. d. enf. **41**:216 (April) 1938.

An exhaustive demographic report is submitted by the chief of a medical mission from the faculty of the University of Paris to Japan, 1936 to 1938.

Among the observations particularly emphasized are: 1. The striking parallelism in statural growth between French and Japanese babies up to 2 years; the more rapid ponderal growth of French infants and the similarity in skeletal development. 2. The morbidity and mortality rates are notably higher for Japan, the chief sources of the increase being tuberculosis, parasitoses, beriberi, gastrointestinal disorders and acute infections of the respiratory system. AMESSE, Denver.

AMOUNT OF BROMINE IN THE BLOOD AND IN THE SPINAL FLUID OF NORMAL CHILDREN. I. GATTO, Lattante **9**:99 (March) 1938.

In breast-fed infants (10) the bromine in the whole blood varied between 0.519 and 0.958 mg. per hundred cubic centimeters; in artificially fed infants (10), between 0.558 and 0.838 mg., and in older children (12), between 0.639 and 0.958 mg. These figures are about the same as those found for adults when the same method (Indovina's) is used. The ratio of the bromine in the cells to that in the plasma (5 cases) was between 0.65 and 0.98. In breast-fed infants (5) the bromine in the spinal fluid was between 0.159 and 0.320 mg. per hundred cubic centimeters; in artificially fed infants (7 cases), between 0.159 and 0.320 mg., and in older children (10), between 0.095 and 0.263 mg. HIGGINS, Boston.

# Society Transactions

## PHILADELPHIA PEDIATRIC SOCIETY

JULIAN M. LYON, M.D., *President*

*May 10, 1938*

AIMS C. MCGUINNESS, M.D., *Secretary*

PRACTICAL IMPORTANCE OF SOFT CURD MILK. DR. IRVING J. WOLMAN and DR. L. A. CHAMBERS.

Within the human stomach cow's milk curdles into coagulated masses which may be large or small, depending on a number of factors intrinsic to the milk and extrinsic, in the gastric juices. Formation of curd may be studied by means of an experimental device which subjects milk to conditions approximating those within the human stomach. The curds which form in this apparatus for artificial coagulation can be measured for the total surface exposed to the digestive enzymes. The determination of the size of the curd can be as useful as the test for curd tension.

A satisfactory definition of "soft curd" milk remains to be formulated. Various processes have been developed commercially in order to impart artificial soft curd qualities to market milk. There are two chemical methods, namely, (*a*) the addition of pancreatic or other enzymes and (*b*) the base exchange process. The mechanical methods can be analyzed as (*a*) mechanical homogenization and (*b*) sound wave homogenization. Each has merits and disadvantages. There is urgent need for adequate criteria of standardization and control.

RECENT RESEARCH PERTAINING TO THE GENERAL AND NUTRITIONAL PROPERTIES OF MILK. DR. O. F. GARRETT.

The most important of all human foods is milk. It is practically the only food of the newborn child; it is basic in the diet during the time the child is growing to adulthood, and it forms a large portion of the diet of the adult, either as milk or in such forms as cheese, butter, ice cream and cooked foods. Not only is it the most important food in the normal diet from birth to death, but it almost invariably is the one food called on to sustain and nourish the human body during lapses from good health. Its sugar, fat, proteins, minerals, vitamins and pigments and their unique properties in nutrition have been the subject of unlimited, untiring and unfinished research throughout the world.

The old conception that milk is milk wherever one finds it can no longer hold. The quality of milk from various sources is as variable as the quality of most other foods from different sources. This is just as true of the nutritional quality of milk as it is of the sanitary quality. The term "quality" itself implies possibility of degree. It is for this reason that the efforts of research workers and of many practical dairymen are being directed toward the production of milk of ever finer quality.

Bang's disease, or bovine abortion, in milk cows not only has created a health hazard because of its association with undulant fever in human beings but has been a source of economic loss to the dairyman. Vaccination of calves with strain 19, of low virulence, has met with considerable success in controlling this disease, although this procedure is still more or less in the experimental stage.

The mammary disease known in this country as mastitis has become the source of tremendous losses to dairymen in the form of decreased production of milk and loss of badly infected animals from the milking herd. Various surveys have estimated that between 25 and 40 per cent of the dairy cows in the eastern part

of the United States have infections of the udder in one stage or another. In a large percentage of the cases there may be no health hazard. However, the New Jersey Agricultural Experiment Station has begun an extensive investigation of the whole problem.

The health of the cow and the quality of the milk are dependent to a large extent on the type and quality of feed.

On the assumption that grasses and legumes in their green form are the natural food of the cow, research workers at the New Jersey Station and elsewhere have bent their efforts toward providing this feed throughout the year. Grasses and legumes are now cut and stored for winter feeding by being converted to grass silage with molasses, without being cured into hay as in the past.

The benefits of feeding grass silage not only are economic but are reflected in the quality of the milk produced. That color is an economic factor in the sale of milk has long been known and made use of by competitive dairymen. Its importance as a nutritional factor, however, is just beginning to be realized as the result of recent important research.

Milk produced in the spring of the year, while the cows are in green pastures, is a pleasing golden yellow. This color holds fairly well until the late winter months, when most of it disappears.

Since, as is now known, carotene is provitamin A, the feeding of grass silage during the winter months results in better nutrition of the cow and consequently in milk of better quality, as evidenced by a higher yellow color and a greater potential vitamin A content. Recent research at the New Jersey Station has shown that grass silage is superior to beet pulp, corn silage or alfalfa hay of good grade in maintaining a yellow color in milk.

On the other hand, green feeds, well preserved grass silage and good hay are excellent sources of good flavor in milk if they are fed according to the directions just given. It has been shown recently by Anderson, of Rutgers University, and by others that there is a close relationship between the amount of carotene in the feed and the disappearance of an "oxidized," or "tallowy" flavor from the milk.

The feeding of roughages which have retained a large portion of their carotene during the winter months helps to eliminate this flavor. Grass silage has proved especially good in this respect.

A tallowy flavor in milk may be caused by contamination of the milk with metals such as copper, nickel and iron. Minute amounts of these (as little as one part per million) will cause the trouble. Copper is the worst offender; therefore, it is absolutely essential that all metal surfaces with which the milk is to come in contact should be free from it.

Exposure of bottled milk to sunlight, even for only a few minutes, produces a tallowy flavor. Longer exposure results in a burnt flavor. This phenomenon is perhaps more likely to occur in cold than in warm weather.

When the vitamin C content is high the milk seems to retain its good flavor much better than when the content is low. Unfortunately, there seems little likelihood of increasing this vitamin in milk by feeding. On the other hand, pure vitamin C is being synthesized commercially, and since its cost has greatly dropped recently, perhaps it may be economically added directly to the milk in the same way that vitamin D is being added in some states.

Since milk normally has too low a vitamin C content to provide sufficient protection even though a quart per day is consumed, it seems reasonable to expect that addition of the synthetic product directly to the milk will provide an excellent and constant source of this vitamin.

### DISCUSSION

DR. CHARLES F. CHURCH: As physicians we are interested in three questions regarding milk: Is it clean? Is it safe? To what extent does it meet the nutritional requirements of man?

Clean milk implies healthy cows; the environment must be so sanitary that the product is kept clean, and the distribution must be maintained in a sanitary manner.

Safe milk implies that bacteriologic and other contaminations of milk are at a minimum. In this country bovine tuberculosis has almost ceased because of the satisfactory control of most of the larger herds, but this is not true in England, for instance, where bovine tuberculosis is a major problem. As to Bang's disease: While the organism was discovered in 1895, it was not until 1924 that the connection between Brucella abortus and undulant fever was made; now the diagnosis of undulant fever in man is made increasingly. In the period from 1924 to 1929, 250 milk-borne epidemics of the disease were reported in this country. These involved 10,000 patients, with 371 deaths. Typhoid fever was the main disease, accounting for 177, or about 74 per cent of these deaths. Thus it is apparent that in the milk-borne epidemics there are other factors than the health of the cows, because typhoid fever is not transmitted by cows. Handling of milk is of primary importance. This does not much concern the large cities; but in smaller communities, where milk distributors have small plants not subjected to sanitary control such as that employed in the larger distribution plants, it is certainly a hazard. Pasteurization, while it is one of the most important safeguards against the unsanitary quality of milk, is a protection only if applied at the right point; in other words, after the contamination has taken place. If the contamination takes place after pasteurization the process is no help whatever. Seventy-one per cent of these 250 epidemics were due to the presence of the disease in the dairy farm or the distributing plant.

As to the nutritional requirements of milk, a number of researches on the quality of the proteins in cow's milk and in human milk have shown the two to be practically identical. There is one exception, however, and that is the amount of cystine. Practically all the cystine present in cow's milk is in lactalbumin. Cow's milk contains relatively little cystine, and in order to make cow's milk equivalent to human milk it would be necessary to add this substance. This may be of practical importance, although not necessarily. The minerals calcium and phosphorus are present in such prominent amounts that it is almost impossible, as all know who have attempted to calculate diets without milk, to obtain a diet that is satisfactory in calcium and phosphorus without including milk or milk products. There is a good reason for not making milk the vehicle for all the requirements of man. As Dr. Garrett has stated, the addition of copper or iron alters the flavor.

The importance of the size of the curd certainly cannot be overestimated, for it has a direct relation to the digestibility of milk. I believe that Dr. Wolman would say that this remains to be proved. There is evidence that the size of the curd is an important factor in digestibility. The flavor of the milk has received attention, and I need not go into that again. Of particular interest is the effect of milk and other dietary ingredients on resistance to infection. There is as yet comparatively little evidence on this point. Wilson in a recent paper in the *Journal of Dairy Research* compared the effect of raw and that of pasteurized milk on resistance of mice to infection and found there was no difference in the two.

DR. PAUL B. CASSIDY: In St. Vincent's Hospital in this city, up to 1926 a fair grade of pasteurized milk was used, and a large number of deaths resulted from gastroenteritis. In 1926 certified milk was secured, with a great reduction of such deaths.

DR. J. D. LEEBRON: Dr. Garrett, does the type of cow make any difference in the milk? The common breeds, I believe, are Ayrshire, Holstein, Guernsey, Jersey and Durham. From personal experience I think that there is some difference.

DR. O. F. GARRETT: So far as flavor is concerned, feed is more important than breed. As far as I know, although I should not want to go on record about this, no one breed produces better milk if fed under like conditions. With regard to flavor and color of milk, the breed does make a difference. Milk of the lowest color comes from the Holstein breed, milk which you all know is the lowest in fat. Guernsey cows produce the highest color, even with the same feed. Recently

my co-workers and I attempted to study the carotene in milk and found that carotene depends more on breed than on feed. Some cows convert a small portion of their carotene into vitamin A (the carotene is recognized as yellow color in milk) and then secrete into the milk a larger part. The Holstein cow does the opposite, converting a large portion into vitamin A and secreting into the milk only a small portion. On a pound per pound basis, the Holstein cow produces milk proportionately as high in carotene as the Guernsey with identical feeds. The color is not necessarily an indication of the amount of vitamin A so long as more than one breed is concerned. With one breed only, color is an indication.

DR. LESLIE A. CHAMBERS: The consensus seems to be that milk with a high level of casein and of butter fat (Jersey and Guernsey) likewise has high curd tension and that more dilute milk has lower curd tension.

DR. JOSEPH STOKES JR.: Dr. Garrett, has there been much evidence concerning increase of vitamin B in milk by feeding various foods containing vitamin B? Since in most cases mastitis in cattle is recognized, has sulfanilamide been tried in treatment?

DR. O. F. GARRETT: Milk is fairly low in vitamin B, including $B_1$. As for effective feeding, I do not know of any results whatsoever. Apparently vitamin $B_1$ is not essential for cows. If it is, they probably do not depend much on feeds for it and apparently do not put much of it into milk.

As for the second question, sulfanilamide has been studied. Just this week or last an article appeared giving first hand information. Our experience has been that the results were absolutely negative. I might say they were worse than that, for we killed 2 or 3 good animals with this drug. Since that time we have learned more about it. Extensive studies have been carried out at State College in connection with the Merck Institute. In the light of some of the knowledge gained and some of the general knowledge applied to human beings, perhaps there is some progress in destroying streptococcic infections in the udder. I do not know just what advance has been made. We gave too massive doses when we started working with animals with definite mastitis. There was some destruction of mastitis with decrease in count of the organisms, but at the same time we caused a great increase in fever and a decided decrease in the flow of milk and finally destroyed the animals. In the light of the latest information, however, sulfanilamide may prove to have some practical application in controlling mastitis in cattle.

ADRENAL NEUROBLASTOMA: REPORT OF A CASE AND REVIEW OF THE LITERATURE. DR. JOHN L. REDMAN, DR. HORST A. AGERTY, DR. OTHMAR F. BARTHMAIER and DR. H. RUSSELL FISHER.

This paper was published in full in the November 1938 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 1097.

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## CHICAGO PEDIATRIC SOCIETY

JOSEPH K. CALVIN, M.D., *President*

*Regular Meeting, Nov. 10, 1938*

GEORGE F. MUNNS, M.D., *Secretary*

GROWTH IN PEDIATRIC PRACTICE. CONTRIBUTIONS OF RESEARCH. DR. HAROLD C. STUART, Boston (by invitation).

This article will appear in full in a later issue.

JOSEPH K. CALVIN, M.D., *President*

*Regular Meeting, Dec. 20, 1938*

GEORGE F. MUNNS, M.D., *Secretary*

CIRCUMCISION. DR. DAVID S. HILLIS.

Circumcision is believed to have been performed in the stone age with a piece of stone sharpened for the purpose. It is recorded in the Scriptures that it was divinely enjoined on Abraham and his descendants. The custom was also supported because of its prophylactic and hygienic value. The leaders of the ancient tribes made laws based on observation that their people died from eating certain poisonous shellfish which could not be distinguished from those that were not, that serious illness or death frequently followed the ingestion of hog meat and that balanitis never occurred when the foreskin was amputated. These and similar laws were so valuable that they acquired the force and authority of religious doctrine, if indeed they did not in fact find a place among tenets of the religion.

However useful these laws were at the time, they have no place in present civilization. Shellfish and pork may today be eaten without danger. Proper management of the newborn and modern hygiene render circumcision entirely unnecessary. The reasons advanced for circumcision are that there is less danger that the boy will masturbate; that it is easier to keep the penis clean; that the child is less likely to acquire venereal disease, and that almost all children are circumcised.

The simple procedure of separating the mucous layer of the foreskin from the glans penis and dilating the opening in the foreskin will serve all purposes and will spare the patient the disabilities incident to a mutilating operation. If this is carried out during the first two weeks of life and again, in a few cases, during the next two months, the foreskin can be retracted to a point below the corona and the penis can be bathed to remove the smegma. When the child is old enough to bathe himself he is instructed that cleansing of the glans penis should be a part of his daily routine.

As to the validity of the reasons given for circumcision, practically every normal boy masturbates at some time in his childhood, stopping at or near the age of puberty. If he continues beyond this time it is because of some fault in the stability of his nervous system, which cannot be avoided by circumcision. Though the mucous membrane covering the glans is somewhat thicker in the circumcised, the difference this makes in the hazard of acquiring a venereal sore is so slight that it need not be considered. To circumcise a baby in order to avoid the trouble of bathing the penis or to make him resemble other boys are reasons which should not prevail against the objections to the operation.

The reasons for not circumcising a newborn baby rest on a firmer foundation. The operation not infrequently is done poorly; if too much of both layers of the foreskin is removed, the penis is deformed and painful when in a state of erection. If the foreskin is removed because of irritation, usually caused by an ammoniacal diaper, the lesion is more severe. The operation does not cure enuresis. A certain incidence of hemorrhage results from the operation. The foreskin has a definite physiologic function in that it facilitates sexual intercourse after the age of 50.

A long, redundant foreskin is often regarded as an indication for circumcision. Such a foreskin can be dilated in every case to permit complete exposure of the glans. If the opening is very small, one or two additional dilations may be required during the second month of life; this can be easily done by the pediatrician with a small pair of artery forceps. If adhesions between the foreskin and the glans reform, the layers may be separated by sweeping a small blunt probe around over the surface of the glans. Such adhesions are not scar tissue.

It is believed that when the obstetrician gives this question the amount of consideration it deserves he will advise against circumcision. The moral support of the pediatrician will be needed to assist in overcoming the opinion of the parents that it should be done, and it may be necessary for him to dilate the opening once or twice after the baby is in his hands.

In view of the many notable improvements in infant mortality and morbidity that have been achieved in the last two decades, it seems timely to add to the list this refinement in the care of the newborn boy.

DISCUSSION

DR. ARTHUR H. PARMELEE: This paper is timely. It is important for physicians to have some uniformity of attitude toward the question of circumcision. I am frequently asked, and I know others are, whether or not the baby should be circumcised. I am particularly disturbed when the mother says: "My doctor said he did not want to circumcise the baby while in the hospital but would like us to bring him back in a few weeks or a month to be circumcised." This attitude should be censured. What is the use of subjecting the child to a procedure that is bound to be painful, perhaps requiring an anesthetic, particularly when it is usually unnecessary?

Dr. Hillis spoke of the poor result all too frequently seen. Circumcision is a a minor operation; at the same time it requires considerable skill, and the bad results are a serious indictment of the universal practice of circumcision. It is nearly always unnecessary and is not without a certain amount of risk; the attitude of the pediatrician, at least, should be one of caution in recommending circumcision.

DR. HENRY E. IRISH: I think there is one method that has not been mentioned. First, there is the surgical operation; second, the abrupt forced retraction, and third, a procedure which seems to be applicable to a considerable portion of the infants who have not been circumcised. I have found that it works well, without any trauma. I instruct the mother to retract the foreskin gradually each day at the time of the bath. I give any necessary aid in divulsion at the monthly health examinations. To the best of my knowledge retraction can be accomplished for practically all infants before the end of the first year with little pain and without harm. I see no reason for removal of the smegma. It is put there for the useful purposes of asepsis and lubrication, and I do not disturb it unless there is some evident irritation.

DR. MANDEL L. SPIVEK: I have been interested in this problem and have watched it closely for a long time. It seems to me that phimosis in the newborn is normal. Practically all newborn babies have the condition. If the foreskin can be retracted with ease, that is not normal. As the baby grows older the opening gradually become more elastic. At Children's Memorial Hospital all babies were referred to a circumcision clinic, where circumcision was discouraged and the foreskin was retracted instead.

DR. DAVID S. HILLIS: The time to perform circumcision, if it is done, is on the eighth day of life. This day is prescribed by the Mosaic law, and studies of the clotting and bleeding time made a few years ago indicated that there is less danger from hemorrhage on the eighth day than on any day preceding or following it. This is an interesting fact to illustrate the accuracy of the old time methods of trial and error. There can be no advantage in delaying the circumcision for two or three months if the baby is in good condition and above 5 pounds (2.268 Gm.) in weight on the eighth day.

I have had no experience with gradual dilation by retraction at frequent intervals over a year. If the mother has the patience to do this it might be even better to do the dilation at one sitting. All foreskins are adherent to the glans at birth, but there is great variation in their length. In 1 case I saw complete absence of the foreskin of an otherwise normal organ, but a long, redundant foreskin is no valid reason for circumcision.

WELTMANN REACTION AND SEDIMENTATION RATE IN RHEUMATIC FEVER OF CHILDHOOD. DR. REUBEN I. KLEIN, DR. SAMUEL A. LEVINSON and DR. PHILIP ROSENBLUM.

The Weltmann serocoagulation reaction and the sedimentation rate were compared in 118 cases of rheumatic fever of childhood and in 10 cases of subacute bacterial endocarditis.

The 118 cases of rheumatic fever were divided into 30 cases of chorea, 33 of acute rheumatic arthritis without carditis, 42 of acute carditis with or without chorea or arthritis and 13 of cardiac decompensation.

The sedimentation rate in chorea, although usually normal, may at times be increased. This increased sedimentation rate may be related to a previous infection. The Weltmann reaction in chorea is almost always either normal or increased.

Acute rheumatic arthritis and carditis are characterized by a rapid sedimentation rate and a low coagulation band. The coagulation band returns to a normal level earlier than the sedimentation rate.

With cardiac decompensation the sedimentation rate tends to slow; the coagulation band is low, normal or high, depending on whether the decompensation overshadows the infection or vice versa.

The three pathologic stages of rheumatic fever, exudative, proliferative and fibrotic, are reflected in the Weltmann reaction.

An increased sedimentation rate does not always mean that the rheumatic infection is active. When the exudative stage of rheumatic fever is over, the patient may be convalescing in what is pathologically the proliferative stage.

The Weltmann reaction is thus of value in the study of rheumatic fever, complementing the sedimentation rate.

In subacute bacterial endocarditis the sedimentation rate is of no diagnostic or prognostic value, whereas the Weltmann reaction may be of aid in the differentiation of the condition from acute rheumatic carditis.

DISCUSSION

DR. P. ROSENBLUM: Dr. Klein has done a great deal of work on this subject. I have had the opportunity of observing most of the patients. The Weltmann reaction certainly is not meant to be taken as the only diagnostic sign, any more than one would make a diagnosis from the white blood cell count only, but it is an interesting clinical adjunct. In the Cook County Hospital, when there were many patients with cardiac involvement and wards were crowded for space, it gave added information which was useful in permitting early discharge. It seems to be of greatest value in childhood, as one does not have to contend with the chronic fibrotic changes that occur in the adult, which may give conflicting results.

DR. STANLEY GIBSON: If I understand the essayist correctly, he has looked on the proliferative process in rheumatic fever as an evidence of healing. I wonder whether one is justified in making this assumption. It is well known that the exudative and the proliferative manifestations may be going on at the same time. If one is to make mistakes in determining the establishment of convalescence in rheumatic heart disease, it is safer to stay on the conservative side. For that reason I feel that the Weltmann reaction should be thoroughly studied before it is considered a safe criterion of cessation of active infection.

DR. R. I. KLEIN (closing): With respect to whether proliferative changes are going on, the only way that can be determined is by the Weltmann reaction. Generally speaking, from a pathologic standpoint the proliferative process is reparative, is the end stage of inflammation and precedes fibrosis or formation of scar tissue. Although there may be so much cardiac damage that during the proliferative stage the patient is just as ill or even more so than he was in the acute exudative stage, it is difficult to see how the proliferative stage can be one of active infection when it means healing. Of course both the proliferative and the exudative stage may be present at the same time. In such an instance

the Weltmann reaction will be neutralized by both the proliferative and the exudative process. That is why one does not rely entirely on it. The general condition and the pulse rate of the child may be sufficient reason to keep him in bed, but it seems to me incorrect to speak of the infection as still active because the rheumatic process is in the proliferative stage and the child has a rapid sedimentation rate. As I have pointed out, the rapid sedimentation rate may merely mean that the inflammatory process has not yet completely ended. Although the patient may be definitely improved, the sedimentation rate will not become normal until the whole process is stationary.

The technic of the test is relatively simple; only 1 cc. of serum is needed, but care is required in making the calcium chloride solution because the salt rapidly changes weight.

SEDIMENTATION RATE AND BLOOD COUNT OF THE NEWBORN INFANT AS COMPARED WITH THE MOTHER. DR. LOUIS J. BRODY.

I felt it would be desirable to find a laboratory procedure which would aid in determining the amount of trauma inflicted on an infant in its passage through the birth canal. Many physicians have had the experience of finding signs of cerebral hemorrhage several days after delivery, in spite of the fact that the infant looked perfectly normal at delivery. In almost every case of death during or immediately after delivery there are foci of hemorrhage in the periosteum, dura and pia. It is assumed that in the healthy newborn child there are various degrees of hemorrhage and destruction of tissue. This naturally results in a certain amount of absorption of products of decomposition. The degree of hemorrhage and the extent of destruction of tissue are extremely varied. Consequently, there should be a difference in the amount of absorption of the protein decomposition products. It may be assumed, then, that in cases in which labor was difficult or in which surgical procedure was necessary the amount of absorption of protein is great and thus the sedimentation rate is high.

In this study, check was made of the following items:

1. The sedimentation rate of the infant on the second and the eighth day after delivery.

2. The blood picture of the infant on the second and the eighth day after delivery.

3. The differences between the sedimentation rate of the mother and that of the child for these two periods.

4. The existing relation between the blood picture of the child and that of the mother.

This study was conducted at Woodlawn Hospital for almost a year; a total of 269 cases were studied. Of this group only 210 were acceptable, owing to incomplete records for either the mother or the infant.

SUMMARY

1. The sedimentation rate of the newborn infants, with few exceptions, varied between 2 and 4 mm. per hour.

2. Cesarean section, low, mid or high forceps delivery, breech delivery and protracted labor had no influence on the sedimentation rate.

3. There was marked variation in the sedimentation rate of the mother, and invariably the rate was higher on the eighth day than on the second. The highest sedimentation rates were found in cases in which no special pathologic condition was perceptible in the mother.

4. The white and red blood cell counts were of no specific aid in determining severity of labor or damage to the child. The subjects with a high sedimentation rate did not necessarily have a high blood count.

5. The greatest changes in the sedimentation rates of the newborn infants were found in those cases in which there was marked loss of weight or failure to regain the initial loss, brought about by vomiting or by some congenital anomaly.

# Book Reviews

**Fundamentals of Dentistry in Medicine and Public Health.** By John Oppie McCall, D.D.S., director of the Murry and Leonie Guggenheim Dental Clinic, Consultant in Dentistry, the New York Hospital, New York. Price, $2.75. Pp. 161, with 50 illustrations. New York: The Macmillan Company, 1938.

The volume is easily read, and the cuts, particularly those of Kronfeld, Box, Bödecker and Appelbaum, are excellent. The purpose, as indicated by title and preface, is to furnish, in compact form, basic information about the teeth for the medical student, physician, nurse and public health worker; in the light of the available satisfactory textual material this is most commendable. There is a grave question whether in attempting to address an audience whose background varies from relatively little to complete medical training Dr. McCall has not attempted a well-nigh impossible task. It is my opinion that the real need for better understanding of dental matters by the medical profession can best be attained through a presentation similar to that in medical texts. In the end, dental physiology, embryology, histology, gross anatomy and pathology comprise no more than a regional division of the broader aspect of medicine. The book is more technical than necessary for the lay reader and too casual for a text used contemporaneously with those devoted to medical subjects.

The organization of subject matter adheres but loosely to the chapter headings. Chapter 1, on embryology, devotes the first 4 pages to histology and concludes with both pathology (hypoplasia and caries) and physiology (teething and the permanent dentition). Chapter 2, on histology, adheres more rigidly to the subject, giving a good superficial exposition of the microscopic anatomy of the tooth. The supporting structures are ignored. The discussion of dental caries in chapter 3 is essentially sound but contains loose statements; this is exemplified on page 58, where hereditary immunity to the disease is confused with environmental influence. In addition, the inclusion of erosion and abrasion in this chapter is somewhat irrelevant. No distinction is made between abrasion and attrition.

The close association of dental and general health, stressed in chapter 6, entitled "Diet, Dental Health and General Health," and the suggestion that the dental structures may prove to be a useful measure of metabolic status point the way to a fertile field for dental-medical cooperation. There is a well founded discussion of the pulpless tooth, but there is no good reason for consideration of Ludwig's angina in this chapter.

The last two chapters, dealing briefly with the general aspects of dental hygiene and public health, are well founded on sound practice. A brief bibliography and a useful glossary are appended.

**Immunity: Principles and Application in Medicine and Public Health.** By Hans Zinsser, M.D., John F. Enders and LeRoy D. Fothergill, M.D. Fifth edition. Price, $6.50. Pp. 801, with no illustrations. New York: The Macmillan Company, 1939.

In this edition, the book formerly entitled "Resistance to Infectious Diseases" has been completely rewritten. It reflects the changed attitude of scientist and physician toward the subject of immunity and resistance to disease. Instead of being the basis of a rather specialized abstract branch of biologic science which interested chiefly laboratory and research workers, immunity has become a practical tool of the newer type of physician, who wants to know why and how the animal body reacts to diseases caused by various agents, including those of bacterial, virus and protozoan origin. The doctor who understands the basic principles of immunity and the fast accumulating knowledge in this field is better equipped to fight disease.

With these facts in mind, the authors have admirably presented their subject matter. The first section, comprising sixteen chapters, deals with the principles and theory of immunity. It contains up-to-date knowledge concerning antigens, toxins, antibodies, agglutinins, hypersensitivity and other basic phenomena.

The second section, consisting of fourteen chapters, presents special problems regarding individual infections. It includes discussions on diphtheria, whooping cough, scarlet fever, meningitis, pneumonia, typhoid fever, syphilis, tuberculosis, virus and protozoan infections and other diseases. Methods of prophylaxis, diagnosis and treatment are given critical evaluation. The pediatrician and the public health officer, as well as the general practitioner, will find this section of the book extremely valuable.

In a review it is impossible to mention all the points which will appeal to various persons, but this book presents the latest information in an important field, covering both laboratory procedure and the practice of medicine. The authors are to be commended for their fine work.

**Children With Delayed or Defective Speech.** By S. M. Stinchfield and Edna Hill Young. Price, $3. Pp. 174, with 67 illustrations and 12 tables. Stanford University, Calif.: Stanford University Press, 1938.

This small volume graphically analyzes the mechanism of voice production and gives an interesting exposition of the rather simple methods by which speech defects may be corrected. The first half of the book is less engagingly written than the rest and seems in places unnecessarily involved.

Along with hearing defects as a cause of speech difficulties are considered psychologic factors and failure of coordinate development of association centers. It is stressed that what may pass for low mentality in children may be only the failure of the proper development of the patterns of speech and that correction of this may markedly raise the apparent level of intelligence. The point is made that there is a particular period for the easy and normal development of speech but that if the opportunity is postponed by disease, faulty training or mental stress there may later be a refractory period, when training is difficult.

The explanation that stuttering in some cases is a conflict between corrected voice production and earlier faulty habit patterns seems more satisfactory than some of the more abstruse theories. The demonstration of corrective methods, which are illustrated by photographs, should convince the reader that such training is practical and important. This book will repay study by the physician interested in the subject and will aid him in the disposition of patients with speech defects.

**The New-Born Infant: A Manual of Obstetrical Pediatrics.** By Emerson L. Stone, M.D. Price, $3. Pp. 291, with no illustrations. Philadelphia: Lea & Febiger, 1938.

This book, written by an obstetrician, takes a view of the newborn infant entirely different from that of the pediatrician. The first six chapters deal with immediate care, nursing care and technic and artificial feeding. Such matters as resuscitation with which the pediatrician does not usually deal, are explained in greater detail than in the ordinary textbook of obstetrics. The chapter on resuscitation is excellently done, as is that on breast feeding. Practical points of nursing technic are stressed and explained in detail. It is quite true that the mother's nursing of her baby may succeed or fail in this period of supervision by the obstetrician. The author gives advice that well may encourage the young mother to satisfactory breast feeding. There are six concise chapters on the disorders and malformations of newborn infants, and the final chapter concerns the care of premature babies.

The bibliography is well chosen and up to date. The book is well written and attractively bound and printed. It covers the newborn period in an excellent manner and should be of interest to every physician that practices obstetrics as well as to the obstetrician and the pediatrician.

**Die Bierhefe als Heil-, Nähr- und Futtermittel.** By Dr. Julius Schülein. Price, paper 11 marks, cloth 12 marks. Pp. 262, with 22 illustrations. Dresden, Germany: Theodor Steinkopff, 1938.

The first chapter of this book, which presents the therapeutic and nutritional aspects of brewers' yeast, is devoted to its history in nutrition. This subject is followed by differentiation of the various types of yeast. There are extensive discussions of such important constituents as vitamins $B_1$, $B_2$ and E, provitamin D, the amino acids and the minerals. A special section is devoted to glutathione. There are some interesting comments on yeast as a factor of diets in hospitals, institutions and the army. The addition of yeast to bread and the use of yeast extracts are discussed. The role of yeast in veterinary therapy and the use of this substance as a fodder are described.

The discussion of yeast as a therapeutic agent is confined to an enumeration of diseases for which yeast or the different vitamins contained in it have been used, including not only diseases that are admittedly due to lack of vitamins but a long list of pathologic conditions for which yeast is supposed to be helpful or of favorable influence. The list is too inclusive, and many of the statements in this chapter must be considered hypothetic. The pediatrician will regret that this section was not treated in a more critical manner.

**Crooked Personalities in Childhood and After.** By Raymond B. Cattell, Ph.D. Price, $2. Pp. 215, with 1 illustration and 1 table. New York: D. Appleton-Century Company, Inc., 1938.

The aim of this book is to give a broad description of modern psychotherapy and clinical management of problem children.

After discussion of the general problem of maladjustment, chapters are devoted to a description of the theories of Freud, Jung and Adler. The author then describes the experimental approach to problems in the clinic, pointing out that the various theories can be fitted together in a scientific biologic background. McDougall's biologic approach to behavior, common nervous energy, Spearman's two factor theory, conditioned reflexes and temperament are described. Additional chapters are devoted to child guidance clinics, the role of the family, maladjustments, genius and society, and psychotherapy.

There are numerous case histories throughout the book. The fact that personality difficulties of adults originate in childhood is emphasized.

The author is a psychologist. In attempting to describe a psychiatric approach to behavior, combining clinical and academic attitudes and covering a wide range of material, he sacrificed some of the unity and practical value of the book.

**The Principles and Practice of Medicine.** Thirteenth edition. By the late Sir William Osler. Edited by Henry A. Christian, M.D. Price, $9. Pp. 1,424, with 15 illustrations. New York: D. Appleton-Century Company, Inc., 1938.

This edition of one of the oldest and best known textbooks of medicine attains the high standard of its predecessors. Because of the death of Dr. McCrae, the present edition was edited by Dr. Christian. Probably no one is better qualified to edit such a book single handed. The advantages of a single author or editor are thus maintained in full.

Not only has the text been brought thoroughly up to date, but there has been considerable rearrangement of material. In my opinion the present form is a marked improvement, probably unduly delayed. Over 200 pages have been added. The text has been made more complete by short descriptions of unusual conditions. The sections on infectious diseases, deficiency diseases and diseases of the blood have been notably revised. Thus, while retaining Osler's style and much of his original material, Christian has succeeded in providing a completely modern edition. Certainly this is one of the finest textbooks of medicine in the English language.

**Vitamin $B_1$ and Its Use in Medicine.** By Robert R. Williams, Sc.D., and Tom Douglas Spies, M.D. Price, $5. Pp. 411, with 19 illustrations. New York: The Macmillan Company, 1938.

With the establishment of the chemical structure of vitamin $B_1$, thiamin, and its artificial synthesis, the time seems particularly appropriate for just such a book as this. Dr. Williams, a doctor of science associated with the Bell Telephone Laboratories of New York, has contributed much to the knowledge of thiamin and is well fitted to discuss the various steps by which this knowledge has developed. Dr. Spies, associate professor of medicine at the University of Cincinnati, has made a special study of the clinical aspects of vitamin deficiencies. Together they have produced a comprehensive and inspiring survey of great value to every physician and student of nutrition.

In the first part of the book is presented rather exact information of immediate value in the practice of medicine. The second part has to do with historical material and experimental study. Both clinical and experimental evidence emphasize the importance of the vitamin to all cellular life. Of great interest is the quantitative relation between the vitamin requirements and the carbohydrate metabolism. Less well worked out, but offering much for the future, is the probable relation of thiamin to enzymatic systems and hormones.

**La mielosi eritremica acuta.** By Angelo Baserga. No price given. Pp. 218, with no illustrations. Pavia: Tipografia Gia Cooperativa, 1938.

The author presents all the principal data available on acute erythremic myelosis, which was first described as a clinical entity by di Guglielmo. A brief history and the nomenclature of the disease are given. The clinical picture is described in detail as to the various organs of the body which are involved. Several chapters are devoted to the blood picture, which is an important phase of the subject. The pathologic picture is also presented. The variations of the disease and its relation to other disturbances of the blood are considered. The etiology and therapy are discussed. The author has added several chapters concerning his research work. The bibliography presents abstracts of 29 case reports with their references. The bibliography contains six pages of additional references. The book will be of greatest interest to those who are studying disturbances of the blood.

**Care of Infants and Children.** By Harry Lowenburg Sr., M.D. Price, $2.50. Pp. 300. New York: Whittlesey House, 1938.

This book contains chapters on prenatal care and instructions for the expectant mother; reasons why the baby should be nursed and the technic of breast feeding; instructions in making up various artificial feedings, menus, and feeding problems of older children; the development of the baby and the hygiene necessary for this development; home care of the child in contagious diseases, and the methods of preparation and administration of various procedures for the sick infant in general. This is a useful and instructive handbook. It in no sense replaces the doctor but simply gives instructions on the methods by which he hopes his orders will be carried out. It is an excellent book to recommend to parents.

**Las vaginitis infantiles.** By Florencio Escardo. No price given. Bound in paper. Pp. 86, with 34 illustrations. Buenos Aires: El Ateneo, 1938.

The author presents general conceptions of the condition and problems of treatment, with an excellent anatomic discussion. He then discusses various forms of therapy, mechanical, chemical and biologic. The methods and results of treatment are well covered. Dr. Escardo favors the type of endocrine therapy advocated by Lewis in 1933. This is discussed in detail, with numerous illustrations from the author's own cases. The plates of histologic sections are excellent. The book should be read in full.

# Directory of Pediatric Societies*

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

### International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 3-5, 1940.

American Committee:
Chairman: Dr. Henry F. Hemholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St., W., Montreal.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

## FOREIGN

### British Paediatric Association

President: Dr. Hector C. Cameron, 23 Devonshire Pl., Upper Wimpole St., London, W. 1.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

### Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

### Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

### Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p.m.

### Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

### Sociedad Cubana de Pediatría

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

### Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

## NATIONAL

### American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Edward Clay Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Place: Hotel Chase, St. Louis. Time: May 15-19, 1939.

### American Academy of Pediatrics

President: Dr. H. F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Netherland Plaza Hotel, Cincinnati. Time: Nov. 16-18, 1939.
Region I. Place: Waldorf-Astoria Hotel, New York. Time: June 1-3, 1939.
Region II. Meeting cancelled.
Region IV. Place: Hotel Leamington, Oakland, Calif. Time: April 6-8, 1939.

### American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

### American Pediatric Society

President: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 27-29, 1939.

### Canadian Society for the Study of Diseases of Children

President: Dr. R. R. MacGregor, 142 Wellington St., Kingston, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

### Society for Pediatric Research

President: Dr. L. Emmett Holt Jr., Johns Hopkins Hospital, Baltimore.
Secretary: Dr. A. A. Weech, 3975 Broadway, New York.
Place: Skytop Lodge, Skytop, Pa. Time: April 26-27, 1939.

## SECTIONAL

### North Pacific Pediatric Society

President: Dr. Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

### Southern Medical Association, Section of Pediatrics

Chairman: Dr. Charles E. Conrad, 209-210 Professional Bldg., Harrisburg, Va.
Secretary: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.

### Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

### New England Pediatric Society

President: Dr. Hyman Green, 483 Beacon St., Boston.
Secretary-Treasurer: Dr. Henry E. Gallup, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

### Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

## STATE

### Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.
Place: Montgomery. Time: April 17, 1939.

### Arkansas State Pediatric Association

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.
Place: Hot Springs. Time: January 1939.

### California State Medical Society, Section on Pediatrics

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

### Florida State Pediatric Society

President: Dr. Gilbert S. Osincup, 300 E. Colonial Dr., Orlando.
Secretary: Dr. Warren W. Quillian, 227 Avenue Aragon, Coral Gables.
Place: Concurrent with state association meeting at time of convention.

### Georgia Pediatric Society

President: Dr. Charles Hall Farmer, 553 Walnut St., Macon.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.
Scientific Meeting—Place: Augusta. Time: Jan. 12, 1939.
Business Meeting—Place: Atlanta. Time: April 1939.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. C. V. Calvin, 144 Golden Hill St., Bridgeport.
Secretary: Dr. E. T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

### Indiana State Pediatric Society

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

### Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

### Louisiana State Pediatric Society

President: Dr. Ruth Aleman, 1407 S. Carrollton Ave., New Orleans.
Secretary-Treasurer: Dr. Philip C. de Verges, 312 Audubon Bldg., New Orleans.

### Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 842 Park Ave., New York.

### Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.

### Michigan State Medical Society, Pediatric Section

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

### Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

### Nebraska Pediatric Society

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

### North Carolina Pediatric Society

President: Dr. W. Myers Hunter, 306 N. Tryon St., Charlotte.
Secretary: Dr. J. R. Adams, 412 N. Church St., Charlotte.

### Oklahoma State Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

### South Carolina Pediatric Society

President: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.
Secretary-Treasurer: Dr. William Weston Jr., 1428 Lady St., Columbia.

### Tennessee State Pediatric Society

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Place: Jackson. Time: April 11, 1939.

### Texas Pediatric Society

President: Dr. F. O. Calaway, 3306 Fannin St., Houston.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Houston. Time: May 9, 1939.

### Virginia Pediatric Society

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

### West Virginia State Medical Society, Section on Pediatrics

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

## LOCAL

### Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

### Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

### Bronx Pediatric Society

President: Dr. Samuel T. Levethan, 254 E. 184th St., Grand Concourse, New York.
Secretary: Dr. David Greene, 910 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

### Brooklyn Academy of Pediatrics

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

### Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

### Chicago Pediatric Society

President: Dr. Joseph K. Calvin, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

### Dallas Pediatric Society

President: Dr. Harold Nesbit, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

### Detroit Pediatric Society

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140–2d Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

### Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St., N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. James H. Park Jr., 3717 Main St., Houston, Texas.
Secretary-Treasurer: Dr. Thomas J. Donovan, 2418 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. Urban Busiek, 200 E. Pershing St., Springfield, Mo.
Secretary: Dr. Fred Speer, 2700 Parallel Ave., Kansas City, Kan.
Place: Kansas City General Hospital. Time: On call.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sidney D. Kramer, 61 Eastern Parkway, Brooklyn.
Secretary: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: Third Wednesday of each month, October to May.

### Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry H. Donnally, 1612 I St., N. W., Washington, D. C.
Secretary-Treasurer: Dr. Harry A. Spigel, 2647 Connecticut Ave., N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St., N. W. Time: 8 p. m., fourth Thursday of October, January, February, March and April.

### Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

### Milwaukee Pediatric Society

President: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Secretary-Treasurer: Dr. Samuel E. Kohn, 425 E. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Lucy Porter Sutton, 168 E. 74th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Northwestern Pediatric Society

President: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Secretary-Treasurer: Dr. R. E. Nutting, 205 W. 2d St., Duluth, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

### Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

### Philadelphia Pediatric Society

President: Dr. Samuel Goldberg, 4546 N. Broad St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

### Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

### Richmond Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., first Thursday of each month, except July, August and September.

### Rochester Pediatric Society

President: Dr. J. Merrel Parker, 11 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

### St. Louis Pediatric Society

President: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: Third Friday of each month from September to June.

### Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

### Southwestern Pediatric Society

President: Dr. Philip E. Rothman, 3875 Wilshire Blvd., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. Clement Smith, 1101 Beacon St., Brookline, Mass.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: Horace H. Rackham Graduate School, Ann Arbor, Mich. Time: Nov. 11-12, 1938.

### Westchester County Medical Society, Pediatric Section (New York)

President: Dr. Norman Survis, 650 Main St., New Rochelle.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.